FORMULATION AND *IN-VITRO* EVALUATION OF LIQUISOLID COMPACT OF PIOGLITAZONE HCL

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Submitted By
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MAY-2018

CERTIFICATE

CERTIFICATE

This is to certify that the dissertation entitled **"FORMULATION AND *IN-VITRO* EVALUATION OF LIQUISOLID COMPACT OF PIOGLITAZONE HCL "** is a bonafide work done by **Mr.S. ZAMEER (Reg.No:261611309), Department of Pharmaceutics, College of Pharmacy, Madurai Medical College** in partial fulfillment of The Tamil Nadu Dr.M.G.R Medical University rules and regulations for award of **MASTER OF PHARMACY IN PHARMACEUTICS** under my guidance and supervision during the academic year 2017–2018.

Name & Signature of the Guide

Name & Signature of the Head of Department

Name & Signature of the Dean/Principal

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CONTENTS

LIST OF ABBREVIATIONS

LSC	:	Liquisolid compressibility test
LSF	:	Liquisolid flowability test
R	:	Excipient (solid) ratio
Q	:	Weight of carrier excipient
q	:	Weight of coating excipient
W	:	Weight of liquid vehicle
CW	:	Net liquid/ solid weight composition (w/w)
Φ value	:	Flowable liquid-retention potential value
Ψ number	:	Compressibility liquid-retention potential number
Ψ Lf	:	Compressible liquid load factor
Φ Lf	:	Flowable liquid load factor
Ψmix	:	Compressibility liquid retention potential of the powder system
Lo	:	Optimum load factor
qo	:	Optimum quantity of coating material
Qo	:	Optimum quantity of carrier material
Wo	:	Optimum weight of non-volatile liquid
Φ ca	:	Flowable number of carrier material
Φ co	:	Flowable number of coating material
Ψ ca	:	Compressible number of carrier material
Ψ co	:	Compressible number of coating material
%	:	Percentage
^{0}C	:	Celsius
cm	:	Centimeter
FT-IR	:	Fourier transform infrared
gm	:	Gram

Hrs	:	Hours
IP	:	Indian Pharmacopoeia
KBr	:	Potassium Bromide
Log	:	Logarithm
mg	:	Milligram
ml	:	milliliter
mm	:	Millimeter
nm	:	Nanometer
µg	:	Microgram
pH	:	Potential of Hydrogen
RH	:	Relative Humidity
Rpm	:	Revolution per Minute
UV	:	Ultra Violet
DSC	:	Differential Scanning Colorimetry
PXRD	:	Powder X ray Diffraction
IR	:	Infra red
λmax	:	Maximum Absorbance
BCS	:	Biopharmaceutical Classification System
Conc.	:	Concentration
CDR	:	Cumulative Drug Release
e.g.	:	Example
Etc.	:	Excetra
FDA	:	Food and Drug Administration
mts	:	Minutes
ppm	:	Parts Per Million
SD	:	Standard Deviation

CHAPTER-1

INTRODUCTION

INTRODUCTION

Many techniques are being employed for the solubility enhancement of poorly soluble drugs to resolve the bioavailability issue due to inadequate dissolution rate. Various approaches make use of hydrophilic polymers as solubility enhancers acting through a variety of mechanisms such as amorphization, co-solvency, micelle formation or inclusion complexes. These techniques impart many advantageous effects in the formulation development. But usually these approaches show lack of stability and decreasing success rate over a period of storage. One of the remarkable demerits of solid dispersions, glass solutions, eutectic mixtures and inclusion complexes is formation of sticky and hygroscopic mass resulting in the poor flow characteristics]. Due to this set-back, industrial feasibility of the final dosage form becomes very difficult. The liquisolid technology emerged as a new drug delivery system distinguished by its characteristics and ability to deliver variety of drugs. Liquisolid drug delivery system has gained attention of pharmaceutical researchers due to its contribution in the solubility enhancement as well as dissolution retarding approaches depending on the need and design of the formulation. With the liquisolid technology as described and patented by Spireas, a liquid may be transformed into a free flowing, readily compressible and apparently dry powder by simple physical blending with selected excipients. Three major components in the formulation of liquisolid compacts are liquid medication, carrier and coat material. Other excipients such as use of disintegrant or release retarding polymers for modification of release profile are used as per the objective and need of the formulation. The first component i.e. liquid medication can either be a liquid drug, a drug suspension or a drug solution in suitable non-volatile liquid vehicles. Inert,

preferably water-miscible organic solvent systems with high boiling point such as propylene glycol, liquid polyethylene glycols or glycerin are best suitable as „liquid vehicle". The solubilization of the drug in a non-volatile solvent keeps the drug in uniformly and molecularly dispersed form. This creates opportunity to enhance the drug release. The liquid medication is incorporated into the second component of the system i.e. the porous carrier material. Once the carrier is saturated with liquid, a liquid layer is formed on the particle surface which is instantly adsorbed by the third component i.e. coat materials. Thus, an apparently dry, free flowing and compressible powder is obtained. Usually, microcrystalline cellulose is used as carrier material.The third component i.e. coat material avoids the re-aggregation of the liquisolid particles and imparts higher flow characteristics. The coating also assists the drylooking character of the system. Many times, amorphous silicon dioxide (colloidal silica) is used as coating material.. Liquisolid formulation containing a drug solution or drug suspension of poorly soluble drugs in a solubilizing vehicle shows enhanced drug release due to increased surface area of drug available for release, increased aqueous solubility of the drug by co-solvency and improved wettability of the drug particles.Accordingly, this improved drug release may result in a higher drug absorption in the gastrointestinal tract and thus, an improved oral bioavailability

HISTORICAL DEVELOPMENT:

Liquisolid technology is the next generation of “powdered solutions” an older technique which was based on the conversion of a solution of a drug in a nonvolatile solvent into a dry-looking, non-adherent powder by mainly adsorbing the liquid onto silica having large specific surfaces. However, such preparations have been studied for

their dissolution profiles while being in a powder dispersion form and not as compressed entities, simply because they could not be compressed into tablets. In later developments on powdered solutions, compression enhancers and binders such as microcrystalline cellulose were incorporated in such systems to improve the compactability of the blend. In these investigations, however, large quantities of silica were being used and the flow as well as compression properties of the product were never validated and optimized to the industrial specifications and requirements. Specifically, when such modified powdered solutions were compressed into tablets, they showed significant problems of “liquid squeezing out” and unacceptably soft tablets. Thus the industrial application of such systems was hindered. Liquisolid compacts, on the contrary, show acceptable flow and compressibility and deserve industrial application. In addition, the term “liquid medication” does not only imply drug solutions, as in powdered solutions, but also drug suspensions, emulsions or liquid oily drugs. Therefore, in contrast to “powdered solutions”, the term “Liquisolid compacts” is wider and more general and it may encompass four different formulation systems *viz*. powdered drug solutions, powdered drug suspensions, powdered drug emulsions and powdered liquid drugs. Furthermore, the earlier term “powdered solution” seems to be inadequate even in describing the original systems, since it has not been proven that the drug remains in solution in the liquid vehicle after its deposition on the extremely large powder surface of silica used.

PHARMACEUTICAL APPROACHES TO ENHANCE THE DISSOLUTION OF DRUGS:

1. **Micronization:** In which particle size of solid drug is reduced to 1to 10µ by spray drying or fluid energy mill example: sulpha drugs.

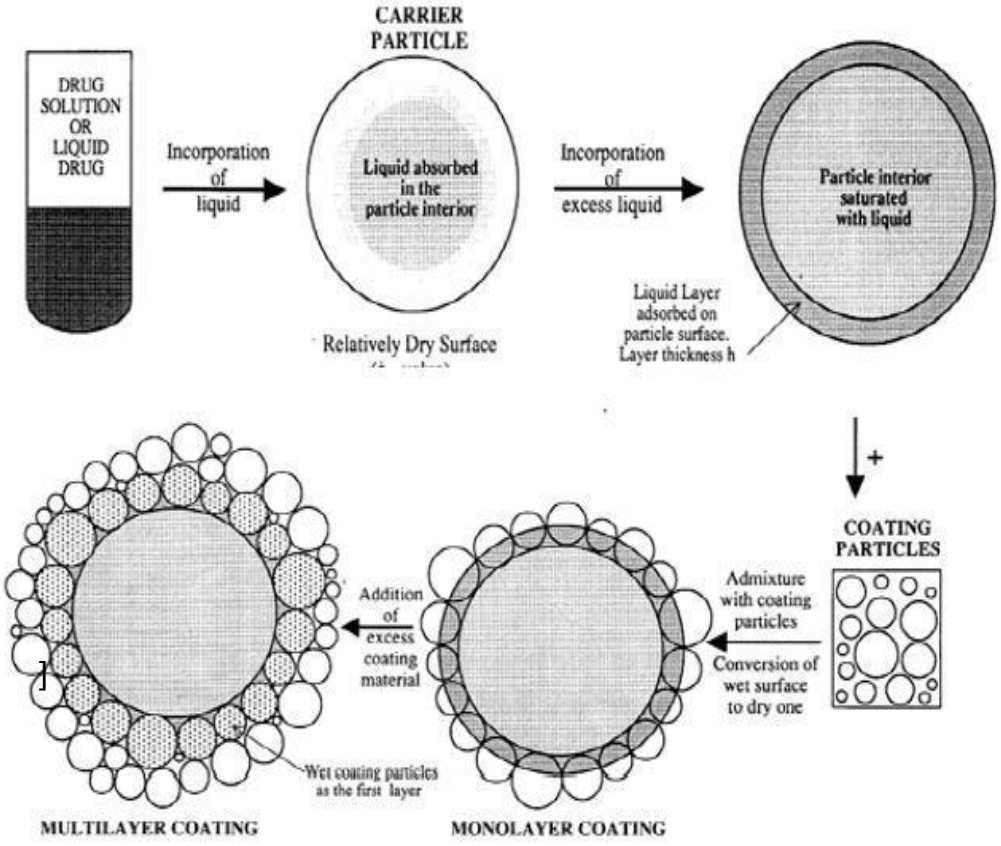
2. **Use of surfactants:** surface active agents enhance the dissolution rate by promoting wetting and penetration of dissolution fluid into solid drug particles example steroids like spironolactone.
3. **Use of salt forms:** salts have improved solubility and dissolution characteristics in comparison to the original drug. Example salt of basic drug like Atropine is more soluble than the parent drug.
4. **Alteration of pH of the Drug Microenvironment:** achieved in two ways in situ salt formation and the addition of buffers to the formulation e.g. buffered aspirin tablets.
5. **Use of metastable polymorphs:** Metastable polymorphs are more soluble than the stable polymorphs of drug that exhibits polymorphism, e.g. chloramphenicol palmitate.
6. **Solute –solvent complexation:** solvates of drugs with organic solvents generally have higher aqueous solubility than the original drug, e.g. 1:2 griseofulvin benzene solvate.
7. **Solvent deposition:** In this method poorly aqueous soluble drug is dissolved in organic solvent and deposited on an inert hydrophilic, solid matrix, e.g. nifedipine is dissolved in alcohol and deposited in starch by evaporation of solvent.
8. **Selective adsorption on insoluble carriers:** A highly active adsorbent can enhance the dissolution rate, e.g. bentonite.
9. **Solid solution-** Use of solid solution: solid solution is a binary system comprising of solid solute molecularly dispersed in a solid solvent. Use of eutectic mixtures: These systems are also prepared by fusion method it is slightly

differ from solid solution in that fused melt of solute –solvent show complete miscibility but negligible solid – solid solubility. The use of solid dispersion: These are generally prepared by solvent or co precipitation method where both guest solute and the solid carrier solvent are dissolved in common volatile liquid such as alcohol. The liquid removed by evaporation under reduced pressure or by freeze drying which result in amorphous precipitation of guest in crystalline carrier.

10. **Molecular encapsulation with Cyclodextrins:** The beta and gamma Cyclodextrins and several of their derivatives are unique in having the ability to form molecular inclusion with hydrophobic drugs having a poor aqueous solubility. These cyclodextrin molecules are versatile in having a hydrophobic cavity of a size suitable enough to accommodate hydrophilic drug as a guest; the outside of the host molecule is relatively hydrophilic. Thus the molecularly encapsulated drug has greatly improved aqueous solubility and dissolution rate. However, among them, the technique of Liquisolid compacts" is one of the most promising techniques. Low cost, simple formulation technique and capability of industrial production serve to be the advantages of this technique.**:**

CONCEPT OF LIQUISOLID SYSTEM

FIG-1:Theoretical concept of liquisolid system



When the drug dissolved in the liquid vehicle is incorporated into a carrier material which has a porous surface and closely matted fibers in its interior such as celluloses, both absorption and adsorption take place. The liquid initially absorbed in the interior of the particles is captured by its internal structure. After the saturation of this process, adsorption of the liquid onto the internal and external surfaces of the porous carrier particles occurs. Then, the coating material having high adsorptive properties and large specific surface area provides the liquisolid system the desirable flow characteristics .In liquisolid systems, the drug is already in solution form in liquid vehicle, while at the same time, it is carried by powder. The wettability of the compacts

in the dissolution media is one of the proposed mechanisms for explaining the enhanced dissolution rate from the liquisolid compacts. Non-volatile solvent present in the liquisolid system facilitates wetting of drug particles by decreasing interfacial tension between dissolution medium and tablet surface. Thus, due to substantial increase in wettability and effective surface area for dissolution, liquisolid compacts may be expected to reveal enhanced release profiles of water-insoluble drugs. Since dissolution of a non-polar drug is often the rate limiting step in gastrointestinal absorption, better bioavailability of an orally administered water-insoluble drug is achieved when the drug is already in solution, thereby displaying enhanced dissolution rates. However, the drug release profile entirely depends on the characteristics of drug, carrier and vehicle used. Thus by altering these variables, liquisolid technique can be used for enhancing or retarding the drug release.

CLASSIFICATION OF LIQUISOLID SYSTEMS:

A. Based on the Type of liquid Medication: Based on type of liquid medication used in the formulation, liquisolid systems may be classified into four subgroups:

1. Powdered drug solutions
2. Powdered drug suspensions
3. Powdered drug emulsions
4. Powdered liquid drugs

The first three may be produced from the conversion of drug solutions or drug suspensions and emulsions, the later from the formulation of liquid drugs into liquisolid systems. Since non-volatile solvents are used to prepare the drug solution or

suspension, the liquid vehicle does not evaporate and thus, the drug carried within the liquid system, remains dispersed throughout the final product. **B. Based on the Formulation Technique:** Depending on the technique used, liquisolid systems may be classified into two categories:

1. Liquisolid compacts

2. Liquisolid microsystems

Liquisolid compacts are prepared using the previously outlined method to produce tablets or capsules, whereas the liquisolid microsystems are based on a new concept which employs similar methodology combined with the inclusion of an additive e.g. PVP, in the liquid medication which is incorporated into the carrier and coating materials to produce an acceptably flowing admixture for encapsulation. The advantage stemming from this new technique is that the resulting unit size of liquisolid microsystems may be as much as five times less than that of liquisolid compacts

MATHEMATICAL MODEL TO DESIGN LIQUISOLID SYSTEM:

The flowability and compressibility of liquisolid compacts are addressed simultaneously in the “new formulation mathematical model of liquisolid systems”. The model can be employed to compute the appropriate quantities of the carrier and coating materials required to produce acceptably flowing and compressible powders. The calculation of composition of carrier, coat and liquid medication is based on new fundamental powder properties called as “flowable liquid retention potential” (Φ- value) and “compressible liquid retention potential”(Ψ-number) of the constituent powder.

The flowable liquid retention potential (Φ-value) of a powder is defined as the maximum amount of a given non-volatile liquid that can be retained inside its bulk (w/w) while maintaining acceptable flowability.

The compressible liquid retention potential (Ψ-number) of a powder is the maximum amount of a given non-volatile liquid, the powder can retain inside its bulk (w/w) while maintaining acceptable compactability, to produce compacts of suitable hardness and friability, with no “liquid squeezing out” phenomenon during the compression process.

The Φ-value of powders may be determined using the liquisolid flowability test. The Ψ-number of powders may be determined by liquisolid compressibility test which employs the „plasticity theories" to evaluate the compaction properties of liquid/ powder admixtures.

The liquisolid flowability test is basically a titration-like procedure in which 25 to 30 g of mixture of the powders under investigation, with increasing amounts of a nonvolatile solvent (i.e. liquid/solid weight composition) are prepared using a standard mixing process. The flow rates and consistencies are assessed using a Recording Powder Flow meter. The liquid/solid weight composition (w/w) in that admixture, which just complies with a desired and preselected limit of acceptable flowability, is taken as the Φ-value of the excipient. The non-volatile solvent used in the liquisolid flowability test should be the one selected to be included in the liquid medication (drug solution or drug suspension) of the targeted liquisolid product. While the study consisting the use of a liquid drug, the liquisolid flowability test should be conducted with the liquid drug itself. This value will change when different solvent or solvent system is employed.

According to the theories, the carrier and coating powder materials can retain only certain amount of liquid while maintaining acceptable flow and compression properties. Hence, the excipient ratio (R) or the carrier: coat ratio of the powder system used should be optimized.

$$R = Q/q \quad (1)$$

R represents the ratio between the weights of carrier (Q) and coating material (q) present in the formulation.

An acceptably flowing and compressible liquisolid system can be prepared only if a maximum liquid on the carrier material is not exceeded. Such a characteristic amount of liquid is termed as Liquid load factor (Lf), which is defined as the ratio of the weight of liquid medication (W) over the weight of the carrier powder (Q) in the system, which should be possessed by an acceptably flowing and compressible liquisolid system.

$$Lf = W/Q \quad (2)$$

The relationship between the powder excipients ratio (R) and liquid load factor (Lf) of the formulations can be given as follows:

$$Lf = \Phi + \varphi\,(1/R) \quad (3)$$

Where, Φ and Φ are the Φ-values of carrier and coat material respectively.

In order to calculate the required ingredient quantities, the flowable liquid retention potentials (Φ-values) of powder excipients were utilized based on reported values in the literature. As from equation 3, Φ and φ and are constants, R and Lf were determined from the linear relationship of Lf versus 1/R to calculate the required

weights of the excipients used. Next, according to the used liquid vehicle concentration, different weights of the liquid drug solution (W) are used. Thus by knowing both Lf and W, the appropriate quantities of carrier (Q) and coating (q) powder materials required to convert a given amount of liquid medication (W) into an acceptably flowing and compressible liquisolid system could be calculated from equation 1 and 2.

COMPONENTS OF LIQUISOLID SYSTEMS:

The major formulation components of liquisolid compacts are:

1. CARRIER MATERIAL

These are compression-enhancing, relatively large, preferably porous particles possessing a sufficient absorption property which contributes in liquid absorption. E.g. various grades of cellulose, starch lactose ,sorbitol, Avicel PH 102 and 200 , Eudragit RL and RS, amorphous cellulose etc.

2. COATING MATERIAL

These are flow-enhancing, very fine (10 nm to 5,000 nm in diameter), highly adsorptive coating particles (e.g., silica of various grades like Cab-O-Sil M5, Aerosil 200, Syloid 244FP etc.) contributes in covering the wet carrier particles and displaying a dry-looking powder by adsorbing any excess liquid.

3. NON-VOLATILE SOLVENTS

Inert, high boiling point, preferably water-miscible and not highly viscous organic solvent systems. Various non-volatile solvents used for the formulation of liquisolid systems include Polyethylene glycol 200 and 400, glycerin, polysorbate 80 and

propylene glycol, propylene glycol, liquid polyethylene glycols, polysorbates, glycerin, N, N- dimethylacetamide, fixed oils, etc.

4. DISINTEGRANT

Superdisintegrants increases the rate of drug release, water solubility and wet ability of liquisolid granules. Mostly Superdisintegrants like sodium starch glycolate and crosspovidone and croscarmellose sodium.

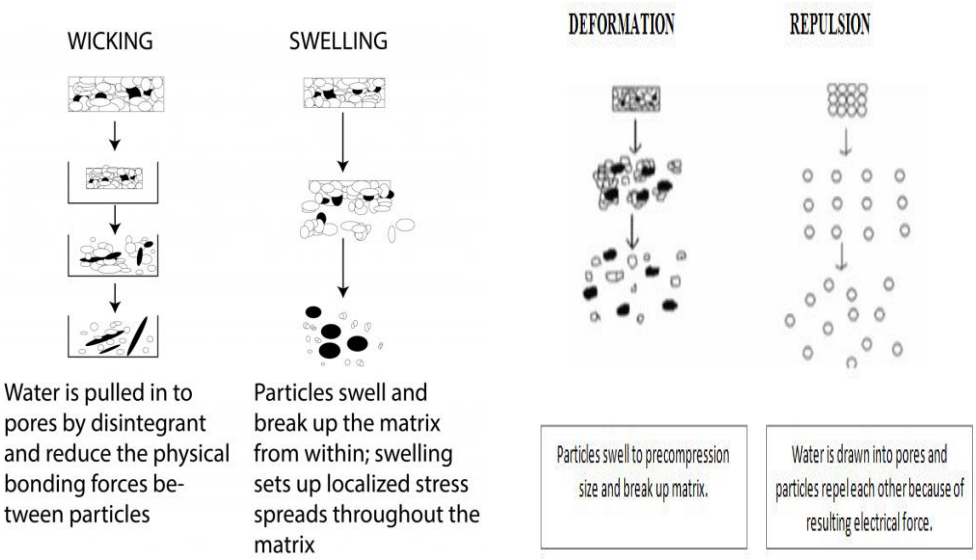


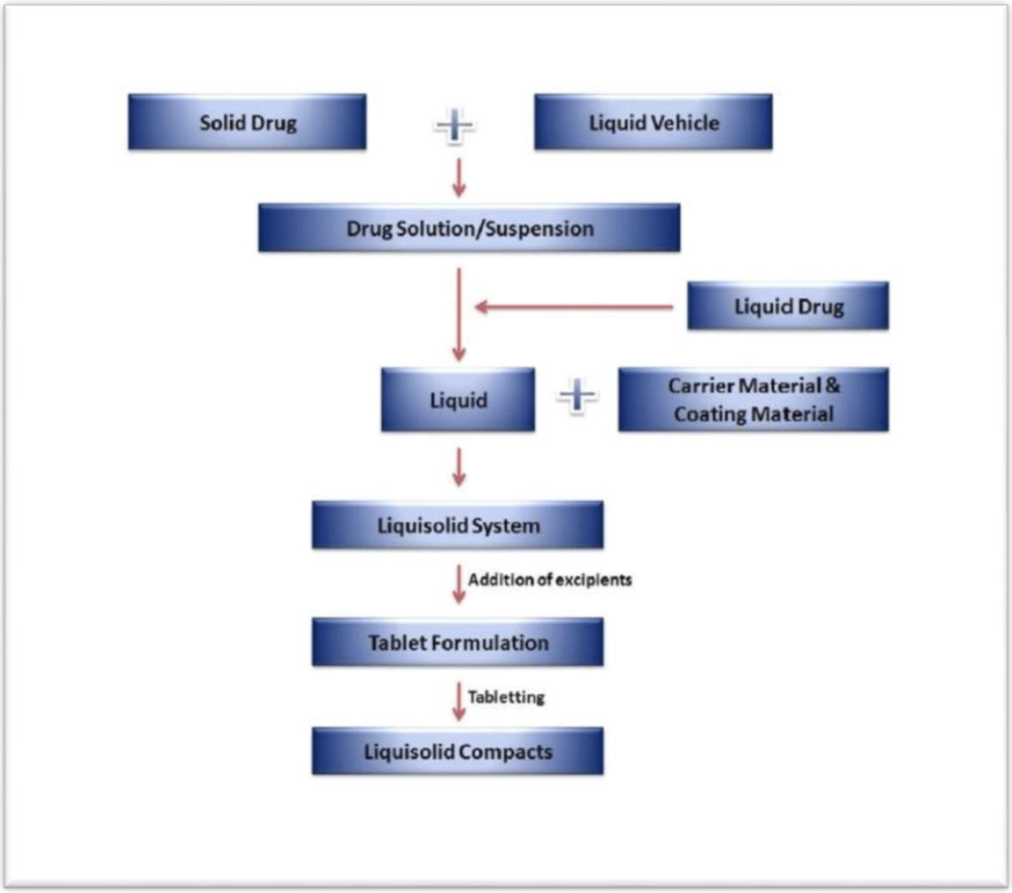
Fig-2: Mechanism of action of superdisintegrants.

PREPARATION OF LIQUISOLID SYSTEM:

As shown in figure, a liquid drug can be converted into a dry-looking liquisolid system without being further chemically modified. If liquisolid system of a solid water-insoluble drug is to be formulated, it should be initially dissolved or suspended in a suitable non-volatile solvent system to produce a drug solution or drug suspension of desired concentration.

Next, a certain amount of the prepared drug solution or suspension or a liquid drug itself is incorporated into a specific quantity of carrier material which should be preferably of a porous nature and possessing sufficient absorption properties. The resulting wet mixture is then converted into a dry-looking, non adherent, free-flowing and readily compressible powder by the simple addition and mixing of a calculated amount of coating material.

FIG-3: Steps involved in the preparation of liquisolid system



Excipients possessing fine and highly adsorptive particles are suitable for this step. Before compression or encapsulation, various adjuvant like lubricants and

disintegrants (immediate release) or binders (sustained release) may be added to final liquisolid system to produce liquisolid compacts i.e. tablet or capsule.

MECHANISMS OF ENHANCEMENT OF DRUG RELEASE:

Several mechanisms of enhanced drug release have been postulated for liquisolid systems. The three main proposed mechanisms include increased surface area of drug available for release, increased aqueous solubility of the drug due to presence of nonvolatile vehicle and improved wettability of the drug particles due to cosolvent effect of the vehicle used.

A.Increased Effective Surface Area: If the drug within the liquisolid system is completely dissolved in the liquid vehicle, it is located in the powder substrate still in a solubilized and molecularly dispersed state. Therefore, the surface area of drug available for release is much greater than that of drug particles within directly compressed tablets. Accordingly, with increasing drug content exceeding the solubility limit and thus, increasing fraction of undissolved drug in the liquid vehicle the release rate decreases. With various drugs it could be shown that the release rates are directly proportional to the fraction of the molecularly dispersed drug (FM) in the liquid formulation. FM is defined by Spireas as the ratio between the drug's solubility (Sd) in the given liquid vehicle and the actual drug concentration (Cd) in this vehicle carried by each system. Therefore,

$$FM = Sd / Cd \quad (4)$$

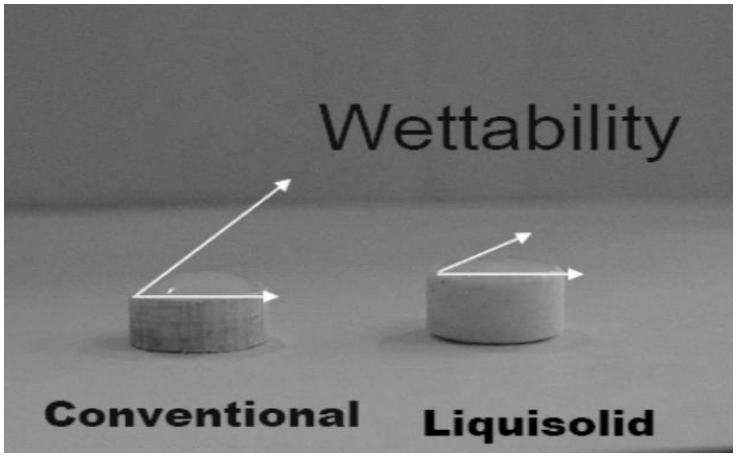
In addition it is thought that the adsorption and absorption of molecularly dispersed drug onto the surface and interior of the carrier particles impart increased

effective surface area available for the mass transfer during the drug dissolution process.

B.Increased Aqueous Solubility: In addition to the first mechanism of drug release enhancement, it is expected that the solubility of the drug might be increased with liquisolid systems. In fact, the relatively small amount of liquid vehicle in a liquisolid compact is not sufficient to increase the overall solubility of the drug in the aqueous medium. However, in the micro-environment of the solid/liquid interface between an individual primary liquisolid particle and the release medium, it is possible that the amount of liquid vehicle diffusing out of a single liquisolid particle together with the drug molecules might be sufficient to increase the aqueous solubility of the drug if the liquid vehicle can act as a cosolvent. The overall increase in the solubility of drugs caused by liquisolid systems was confirmed in various studies.

C.Improved Wetting Properties: Due to the fact that the liquid vehicle can either act as surface active agent or has a low surface tension, wetting of the primary liquisolid particles is improved.

Fig-4: Wetting property of liquisolid system.



Wettability of these systems can be demonstrated by contact angles and water rising times. Also the adsorption of the drug on the carrier particles increases the effective surface area, improving the contact of drug and wettability.

Dissolution studies on liquisolid tablets

Tablets should be sufficiently hard to resist breaking during normal handling and yet quickly disintegrate properly after swallowing.

Dissolution rate (DR) is explained according to the “Noyes – Whitney” equation and “diffusion layer model” dissolution theories.

$$DR = (D/h)\ S\ (Cs - C)$$

According to this equation, stagnant diffusion layer thickness is h, and formed by the dissolving liquid around the drug particles. D is the diffusion coefficient of the drug molecules transported through it, S is the surface area of the drug available for dissolution, C is the drug concentration in the bulk of the dissolving medium, and Cs is the saturation solution of the drug in the dissolution medium. Dissolution tests for liquisolid tablets were done at constant rotational speed and in identical dissolution media, thus allowing estimation of the thickness of the stagnant diffusion layer (h). From this equation, dissolution rate is directly proportional not only to the concentration gradient of the drug in the stagnant diffusion layer (Cs- C), but also to its surface area (S) available for dissolution.

For estimation and comparison, drug dissolution rates (DR) of drug were used, with amount of drug dissolved per min presented by each tablet formulation during the first 10 minutes. (Shashidher Burra *et al*., 2011).

$$DR = \frac{(M \times D)}{1000}$$

Where,

M = Total amount of pure drug in each tablet

D = Percentage of drug dissolved in the first 10 minutes

ADVANTAGES

Liquisolid tables have many advantages. These include:

- Liquisolid systems are low cost formulations than soft gelatine capsules.
- Drug release can be modified using suitable formulation ingredients
- Drug can be molecularly dispersed in the formulation.
- Capability of industrial production is also possible.
- Enhanced bioavailability can be obtained as compared to conventional tablets.
- Several slightly and very slightly water-soluble and practically water-insoluble liquid and solid drugs can be formulated into liquisolid systems.
- Even though the drug is in a tablet or capsule form, it is held in a solubilized liquid state, which contributes to increased drug wetting properties, thereby enhancing drug dissolution.
- Rapid release liquisolid tablets or capsules of water insoluble drugs exhibit enhanced *In-vitro* and *in-vivo* drug release when compared to their commercial counter parts, including soft gelatin capsules preparation.
- Sustained release liquisolid tablets or capsules of water insoluble drugs exhibit constant dissolution rates (zero-order release) comparable only to expensive

Commercial preparations that combine osmotic pump technology and laser-drilled tablets.

- Can be applied to formulate liquid medications such as oily liquid drugs.
- Better availability of an orally administered water insoluble drug.
- Production of liquisolid systems is similar to that of conventional tablets.
- Can be used for formulation of liquid oily drugs.
- Can be used in controlled drug delivery.

LIMITATIONS

- Not applicable for formulation of high dose insoluble drugs.
- If more amount of carrier is added to produce free-flowing powder, the tablet weight increases to more than one gram which is difficult to swallow.
- Acceptable compression properties may not be achieved since during compression liquid drug may be squeezed out of the liquisolid tablet resulting in tablets of unsatisfactory hardness.

APPLICATIONS

- Liquisolid compact technology is a powerful tool to improve bioavailability of water insoluble drugs. Several water insoluble drugs on dissolving in different non-volatile solvents have been formulated into liquisolid compacts.
- Literature cites different drugs successfully incorporated into liquisolid compacts.
- Rapid release rates are obtained in liquisolid formulations.
- These can be efficiently used for water insoluble solid drugs or liquid lipophilic drugs.

- Sustained Release of drugs which are water soluble drugs such as propranolol hydrochloride has been obtained by the use of this technique.
- Solubility and dissolution improvement
- Flowability and compressibility
- Designing of Controlled Release Tablets
- Bioavailability Enhancement
- Application in probiotics.
- The possibility of using liquisolid technique as a promising alternative to conventional coating for the improvement of drug photostability.

CHAPTER-2

LITERATURE REVIEW

CHAPTER - II

LITERATURE REVIEW

Vinod valjibhai siju et al.,(2017) improved the dissolution rate of the drug, cilnidipine (CLD) by using the liquisolid compact technique and wet granulation.cildipine drug is poorly soluble in water and it's highly soluble in higher pH.in this study drug is solubilize in tween 80 and sodium hydroxide and meglumine solution. And then drug solution binding on pearlitol SD 200. PVCP K30 used as a binder and crospovidone used as disintegrant. Sodium hydroxide and meglumine used as a buffering agent for basic media preparation.the drug release rates of tablets which prepared by liquisolid compact have higher solubility and dissolution then conventional tablets.

Mamatha and sulthana.,(2017) developed new formulation to enhance the solubility of a highly permeable and a poorly soluble oral drug antihyperglycemic agent, nateglinide by liquisolid compacts. The liquisolid compact technique is based on dissolving the insoluble drug in propylene glycol, polyethylene glycol 400, tween-80 as non-volatile solvents in which drug is having high solubility and admixture of drug loaded solution with microcrystalline cellulose as carrier, aerosil as coating material, crospovidone as disintegrant, and magnesium stearate as lubricant to convert into acceptably flowing and compressible powder. The prepared liquisolid compacts were evaluated for their flowing properties such as bulk density, tapped density, angle of repose, Hausner's ratio, and Carr's index. Further tablets were evaluated for hardness, thickness, weight variation, friability, disintegration test, and *in vitro* release study. From this higher drug release profiles due to increased wetting property and surface area of the drug available for dissolution was obtained in case of liquisolid compacts. Among all formulations, liquisolid system prepared by propylene glycol was considered as best

formulation which release drug up to 98% in 60 minutes and in comparison to marketed formulation, optimized formulation showed better dissolution profile.

Dias *et al.,(2017)* had prepared liquisolid compacts of high dose water insoluble drug, carbamazepine (CBZ) using novel porous carriers such as Neusilin and Fujicalin in order to improve its dissolution rate and reduce the tablet weight. Solubility of CBZ was determined in different non volatile solvents to finalise vehicle having maximum solubility. The liquid retention potential (Φ) of carriers and coating material was determined and 18 different liquisolid compacts of CBZ were formulated. The prepared liquisolid compacts were evaluated and compared for thickness, diameter, weight variation, uniformity of content, hardness, friability, disintegration and *in vitro* dissolution. Dissolution profile of liquisolid compacts was compared with marketed tablet formulation. The solubility of CBZ in polyethylene glycol 200 was found to be greater than the other solvents. Neusilin showed higher Φ value than traditional carriers. Formulated liquisolid compacts showed all physical parameters within prescribed limit. Formulation containing Neusilin-Neusilin and Neusilin- Aerosil showed no disintegration while all other formulations showed disintegration up to 180 seconds. All the formulations showed drug release above 80% at the end of 15 minutes except marketed formulation. The weight of formulations containing Neusilin and Fujicalin ranged in between 0.383-0.947g. Formulation FA3 containing Fujicalin exhibited lower mean dissolution time and higher dissolution efficiency than all other formulations including marketed tablet.

Mustafa E *et al.,* (2017) had designed orodispersible tablets of zolmitriptan by using liquisolid technique. Orodispersible tablets were prepared by using propylene

glycol, avicel PH-102 and aerosil 200 as a non-volatile solvent, carrier material and coating material respectively and various types of super disintegrating agents such as croscarmellose sodium, sodium starch glycolate, and crospovidone to facilitate faster disintegration of the liquisolid compact.

The overall results showed that among the three super-disintegrants, crospovidone was the best super disintegrant showing the shortest disintegration time while loading factor of 0.125 was the best in the preparing of zolmitriptan liquidsolid orodispersible tablets .

Patil,et al.,(2016) formulated and evaluated liquisolid compact system of carvedilol to give increased dissolution rate of drug by utilizing PEG400 as the non-volatile liquid vehicle. The liquisolid tablets formulated with PEG400 at different concentrations and the suitable analytical method based on UV-visible spectrophotometer was developed for carvedilol. The results of differential scanning calorimeter and Fourier transform infrared analysis confirmed that the excipients are compatible with the drug. The liquisolid tablets formulated with PEG400 at drug concentration 20% w/w is the best formulations among the other 10 batches of liquisolid tablet prepared, in terms of superior dissolution profile. LSC3 with *R* value 15 gave the maximum drug release. Short term accelerated stability study of optimized formulation (LSC3) of carvedilol was carried out at 40°C ± 2°C and at 75% ± 5% RH for 1 month.

Padmapreetha J *et al.,* (2016) had formulated liquisolid compact to enhance the dissolution rate of leflunomide by using kolliphor EL, avicel PH 102, aerosol, and sodium starch glycolate as a non-volatile solvent, carrier, coating material and super disintegrant respectively. The results showed that during the first 10 min ($Q_{10\%}$) the

optimized formulation released 73.39% of its content compared to 18.94 % of the conventional formulation. In conclusion, leflunomide dissolution rate can be enhancing to a greater extent by liquisolid technique

Mowafaq MG *et al.,* (2015) had prepared liquisolid compact for solubility enhancement of tenoxicam using tween 80 as a non-volatile liquid, avicel PH102 as a carrier, and aerosil 200 as a coating material. Liquisolid formulations containing various drug concentrations in liquid medication ranging from 10% to 35% w/w were prepared. Liquisolid formulations showed greater drug release rates than conventional and marketed tablets due to increasing surface area of the drug and wetting properties.

Zafar et al (2015)., had compared Liquid-solid technique and solid dispersion formation which are two novel approaches for enhancement of dissolution rate of BCS class II drugs. Liquisolid compact converts a liquid drug or drug solution into a free flowing powder with enhanced dissolution rate. In case of solid dispersion drug is molecularly dispersed in a hydrophilic polymer in solid state. In the present study, Liquisolid and solid dispersion techniques were applied to enhance the dissolution of the Hydrochlorothiazide. Three formulations of Hydrochlorothiazide were prepared by Liquisolid technique using micro crystalline cellulose as carrier material and colloidal silicon dioxide as coating material. Water, poly ethylene glycol- 400 and Tween-60 were used as solvent system. Solid dispersions of Hydrochlorothiazide were prepared by solvent fusion method using PEG-4000 as carrier polymer. Tablets were subjected to evaluation of various physical and chemical characteristics. Dissolution profiles of tablets prepared by the novel techniques were compared with marketed conventional tablets. Model independent techniques including similarity factor, dissimilarity factor and

dissolution efficiency were applied for comparison of dissolution profiles. The results obtained indicated that liquid solid compact formulations were more effective in enhancing the dissolution rate compared with solid dispersion technique. The Liquisolid compacts improved the dissolution rate up to 95% while the solid dispersion increased it to 88%.

Ayesha et al (2015)., had prepared Liquisolid compacts using polyethylene glycol 400, propylene glycol and Tween-80 as non-volatile solvents. Neusilin as carrier material and Aerosil-200 as coating material for enhancement of dissolution rate of Olmesartan medoxomil. From the study, it was concluded that the dissolution studies for Liquisolid compacts and conventional formulations were performed and it was found that Liquisolid compacts with Neusilin and Tween-80 showed significant higher drug release than conventional

Prakash et al (2014)., had investigated Liquisolid powder compacts (LSPCs) proved to be the potential solubility improvement strategy for efficient oral delivery of BCS class II and IV drugs. The LSPCs were formulated using propylene glycol as non-volatile solvent. The effect of different formulation variables on LSPCs performance was evaluated using 32 factorial design. The selected independent variables were % of clonazepam in propylene glycol (X1) and % of sodium starch Glycolate (X2) and dependent variables were disintegration time (YDT) and % cumulative drug release at 15th minute (YQ15). LSPCs of CLZ formulated with propylene glycol at optimum drug concentration produced high dissolution profile with acceptable tablet properties. Fourier transform infra-red spectroscopy (FTIR) studies revealed that there was no interaction between drug and polymers, differential scanning calorimetry (DSC) and X Ray

Diffraction (XRD) indicated conversion of crystalline to amorphous form of the CLZ. The permeation studies carried out in isolated rat intestine revealed that potential of LSPCs for enhanced permeation of CLZ across rat intestinal barrier. The increase in permeation of clonazepam from LSPCs formulation across rat intestine suggests the potential of LSPC formulation for improved oral delivery of CLZ. In conclusion, the present study showed that LSPC technique could be a promising strategy in improving dissolution of poorly water soluble CLZ and wettability was improved by making a suspension in propylene glycol, the water soluble, nonvolatile solvent. LSPCs could be prepared using MCC PH 102 as a carrier, and AEROSIL® 200 as a coating material. The FTIR studies revealed that excipients were compatible with the drug. DSC and XRD studies showed that there is a decrease in crystallinity of the CLZ in Liquisolid compact formulation. A fall in crystallinity means improved dissolution release profile. The optimized formulation showed higher dissolution rate when compared with that of pure drug.

Elkordy et al., (2014), had investigate dissolution behavior of norfloxacin as a model hydrophobic drug through application of Liquisolid technology. Norfloxacin was prepared as Liquisolid formulations using either flowability or compressibility Liquisolid tests. The dissolution profiles were evaluated and compared to counterpart conventional norfloxacin tablets. Two non-volatile liquid vehicles were used in the preparation of norfloxacin Liquisolid formulations; Poly Ethylene Glycol (PEG200) and Synperonic PE/L-61. The Liquisolid formulations of norfloxacin were tested according to the specification of British Pharmacopoeia (BP) quality control tests. Moreover, the pre-preparation evaluation tests, such as powder flowability Carr's index, differential

scanning calorimetry (DSC) and Fourier transform infrared (FT-IR), were applied for further investigation of the physicochemical properties of the Liquisolid formulations. The results indicated that the percentage of norfloxacin release in acetate buffer solution (pH = 4.0) is higher than in distilled water. Also, at the first 20 min, the percentage of the drug release is higher only in the decreased amount of liquid vehicle formulations compared with the conventional tablet. Generally, the conventional tablet dissolution profile is either similar or higher than Liquisolid tablets. Moreover, Synperonic PE/L-61 Liquisolid tablets showed higher dissolution profiles than PEG200 Liquisolid tablets, although the solubility of norfloxacin in PEG200 (2.507 mg/ml) is much higher than in Synperonic PE/L-61 (0.167 mg/ml). In conclusion, increasing the percentage of liquid vehicle in the prepared norfloxacin Liquisolid formulations does not necessarily lead to increase in the percentage of the drug release in distilled water dissolution medium

Yousef et al., (2014), had investigated the effect of solvent type on Diltiazem hydrochloride release profile from Liquisolid compacts. To examine aforementioned idea, the drug solubility was studied in several conventional nonvolatile solvents. Liquisolid formulations of diltiazem HCl in the different solvents were prepared and their release profiles were also obtained. Effect of aging on the hardness and drug release profile was studied as well. X-ray crystallography and differential scanning calorimetry (DSC) were used to investigate the formation of any complex between drug and carrier or any crystallinity changes during the manufacturing process. The results showed that diltiazem HCl had lowest solubility in polysorbate 20. Highest amount was devoted to polysorbate 80 and propylene glycol. Type of nonvolatile solvent and its

physicochemical properties as well as solubility of the drug in the applied solvent found to have important role on release profile of the drug from Liquisolid compacts. Hardness and dissolution profile of the drug were not affected by aging. Amorphous form was obtained during the process of Liquisolid formulation. It follows that the optimized new technique can be used to prepare sustained release formulations of water-soluble drugs.

Srinivas et al., (2014), had improved the solubility and dissolution rate of poorly soluble drug Piroxicam by using Liquisolid technique. This technique of delivering drugs is suitable mostly for lipophilic drugs and poorly water soluble drugs. However, an apparent limitation of this technique is the formulation of a high dose because a large amount of liquid vehicle is needed, which finally results in a low-dose liquid solid formulation. This approach is suitable for both immediate and sustained release formulations. Solubility is increased by using non-volatile solvents such as PEG 400, Labrosol, Span20 and Tween 80 in single or combination which are suitable for drug and dissolving the drug in those nonvolatile solvents, which is termed as 'liquid medicament'. The liquid medicament is blended with carriers such as microcrystalline cellulose and Aerosil to convert the liquid medicament into a non-adhering, dry looking powder which has acceptable flow properties and compression behavior. These Liquisolid systems are evaluated by micromeritics studies like flow behavior, bulk density, tapped density, compressibility index, drug content, in vitro release, Fourier transform infra-red spectroscopy and powder X-ray diffraction. He concluded that dissolution rate and bioavailability of poorly water soluble drugs like Piroxicam can increased by applying Liquisolid technology. He also observed, In-vivo drug release

study of Liquisolid compacts using animal model to claim success in the development of Liquisolid compacts of Piroxicam.

Iizhar S. and Bhavani (2014), had studied the effect of carrier: coating ratio, concentration of disintegrant and non-volatile solvents on disintegration time and dissolution rate in the formulation of Liquisolid compacts of Nateglinide. An apparent limitation of this technique is the formulation of a high dose because a large amount of liquid vehicle is needed, which finally results in a low-dose liquid solid formulation. NTG was dispersed in PEG-400 as a liquid vehicle. Then a binary mixture of carrier–coating materials (MCC- Aerosol) was added to the liquid medication under continuous mixing. Precompression studies, such as flow properties were also carried out. The formed mixture was compressed to get tablets matrices by using the tableting machine. The prepared Liquisolid tablets were evaluated by hardness, friability, disintegration test and in vitro dissolution studies. The dissolution property of a water-insoluble drug Nateglinide (NTG) was investigated. The dissolution profile of the prepared Liquisolid tablets was also compared to that of a marketed formulation (MR). The results indicate that Liquisolid based tablets (F3) showed greater disintegration and dissolution rate. It might be due to the presence of PEG-400 as it showed the enhancement in the solubility of NTG. FT-IR results showed compatibility of Nateglinide with excipients used. He concluded that as the carrier: coating ration increases with the concentration of disintegrant, disintegration and dissolution rate of Liquisolid compacts of Nateglinide was increased.

Poluri et al., (2014), had formulated fast disintegrating tablets by using Liquisolid technology. Sodium starch Glycolate, crospovidone are used as superdisintegrant in

this invention to reduce disintegration time by which fast absorption can take place which ultimately increase dissolution of the drug. As a result of comparison with marketed formulation using similarity dis-similarity factor, both formulations shows similar in-vitro dissolution profile of Lamotrigine.

Manish et al., (2014), had developed a novel liquid solid technique which enhances the dissolution rate of water insoluble or poorly water soluble drugs of Nilvadipine, which belong to class II of BCS. Liquisolid Formulations shows better Flowability, Compressibility, improves solubility, dissolution and better absorption. Rapid disintegration rates are observed compared to conventional tablets and therefore, they show improved release rates and hence greater bioavailability. The use of non-volatile solvent in the formulation causes increased wettability of water insoluble drugs and ensures molecular dispersion of drug in the formulation.

Jyothi et al., (2014), had enhanced the dissolution rate of Glyburide which is insoluble in water. Different formulations were prepared by using different vehicles and carriers and Aerosil is used as the coating material. The empirical method as introduced by Spireas and Bolton was applied to calculate the amounts of coating and carrier materials required to prepare glyburide Liquisolid tablets. In vitro dissolution profiles of the Liquisolid formulations were studied and compared with conventional formulation in 0.1N HCl. It was found that Liquisolid tablets formulated with PEG 400 and Avicel pH102 produced high dissolution profile and they showed significant higher drug release rates than conventional tablets due to increase in wetting properties and surface of drug available for dissolution. Drug-excipient interaction studies showed that there is no interaction between the drug and excipients. In conclusion, development of glyburide

Liquisolid tablets is a good approach to enhance the dissolution rate which increases bioavailability.

Ujwala R., Venkateswara R. and Navaneetha (2014), had developed a novel liquid-solid technique to enhance the dissolution rate of candesartan which is poorly water soluble drug which is a BCS class II drug. The selection of non-toxic hydrophilic solvent, carrier, coating excipients and its ratios are independent of the individual chemical entities which is indirectly leads to enhancement of bioavailability. Liquisolid tablets were prepared by using PEG -400, PG as non-volatile liquid vehicles and Avicel PH 102, Aerosil 200 as carrier and coating materials, CCS as super disintegrants respectively. Among all formulations F7 was shown best drug release and result shows increased dissolution profile i.e., 98.1% with polypropylene glycol. The invitro dissolution study confirmed enhanced drug release from liquid solid compacts compared with conventional and marketed tablets.

Hitesh J *et al.,* (2014) had compared liquisolid and inclusion complexation techniques for dissolution rate enhancement of valsartan. This study was designed for screening of suitable non-volatile liquid solvent for the preparation of liquisolid compact such as tween 80, polyethyleneglycol 400 and propylene glycol by using the mathematical equation. The study was also aimed for enhancement of dissolution rate and comparison of liquisolid technique with inclusion complex of β-cyclodextrin. The liquisolid formulation showed highest dissolution rate compared with directly compressed tablet, pure drug, and formulation prepared by complexation technique

Yesubabu B *et al.,* (2014) had formulated fast disintegrating tablets of lamotrigine using different super disintegrating agents such as crospovidone, sodium

starch glycolate. Various batches of liquisolid tablets were prepared. Formulations consisting of sodium starch glycolate were found to be fulfilling all the parameters satisfactorily when compared with crospovidone. *In-vitro,* drug release studies showed that within 30 min almost 90% of the drug was released from all the formulations confirming enhancement of drug dissolution by liquisolid technique

Ahmed S. Abdul Jabbar et al., 2013, formulated and evaluated piroxicam liquisolid compact different liquisolid compacts were prepared using a mathematical model to calculate the required quantities of powder and liquid ingredients to produce

acceptably flowable and compressible admixture. The liquisolid formulation which might be attributed to the formation of hydrogen bonding between the drug and liquid vehicle this resulted in drug dissolution enhancement.

Amal Ali Elkordy et al., 2013, studied spironolactone release from liquisolid formulations prepared with capryol 90, solutol HS-15 and kollicoat SR 30D as nonvolatile liquid vehicles were used in the design of spironolactone liquisolid formulations, capryol 90, synperonic PE/L61 in combination with solutol HS-15 at a ratio of 1:1 and kollicoat SR 30D. Spironolactone liquisolid formulations were tested according to British Pharmacopoeia (BP) quality control tests. Liquisolid powder formulations formulated from a combination of synperonic PE/L61- solutol HS showed highest dissolution. The liquid vehicles used with spironolactone liquisolid formulations enhanced drug dissolution rate.

Jarag Ravindra Jagannath et al., 2013, formulated and evaluated sustained release liquisolid tablets of metoprolol succinate. This is directed towards the development of liquisolid compact for the production of sustained release tablet of water

soluble drug. Liquisolid compacts were prepared by using Tween 80 as the liquid vehicle or nonvolatile solvent. Avicel PH 102 as absorbing carrier and Aerosil 200 as adsorbing coating material. Tween 80 has plasticizer effect by which it can reduce the glasstransmission temperature of polymer and impart flexibility in sustaining the release of drug from liquisolid matrices. The results showed that wet granulation are markable impact on the release rate of drug from liquisolid compacts reducing the release rate of drug from liquisolid compacts.

Gandhi K.J. et al., 2013, formulated, characterized and evaluated the liquisolid tablet containing pioglitazone HCl. The invitro release pattern of liquisolid tablets and directly compressed tablets were studied using USP-2 apparatus. The study concludes that the liquisolid technique is a promising alternative and best suitable method for enhancing solubility.

Pandey A. et al., 2013, carried out project on dissolution rate enhancement of BCS Class II drug paliperidone by spray drying. The technique adopted is very well used industrially for preparing amorphous composition of poorly soluble crystalline drugs. In case of spray drying PAL with different classes of hydrophilic carriers (different grades of polyvinyl pyrolidones [PVPs, plasdones] and cellulosic polymers) were taken. Significant enhancement in dissolution rate was observed with the prepared spray dried compositions and out of three grades of plasdone; plasdone K12 demonstrated the maximum enhancement in rate of release of PAL. Spray drying of PAL with plasdones, especially plasdone K12 reduced drug crystallinity, increased rate and extent of dissolution.

Pande V. V. et al., 2013, enhanced dissolution rate of rosuvastatin calcium by liquisolid compact technique. In this technique, liquid medications of water insoluble drugs in non-volatile liquid vehicles can be converted into acceptably flowing and compressible powders. As liquisolid compacts demonstrated significantly higher drug release rate, they lead to a conclusion that it could be a promising strategy by improving the dissolution of poor water soluble drugs and immediate release solid dosage forms.

Amal Ali Elkordy et al., 2012, performed liquisolid technique to enhance and sustain griseofulvin dissolution effect by using non-volatile liquid vehicles. They studied the effects of different liquid vehicles on release characteristics. Fast dissolution tablets were prepared using three different non-ionic surfactants namely cremophor EL, synperonic PE/L61 and capryol 90; on the contrary kollicoat SR 30P were used for production of sustained release formulations. Avicel PH102 and cab-O-sil M5 were used as a carrier and coating materials respectively. Cremophor EL showed the best dissolution enhancement with % PE of about 90% compared to only 23% of conventional tablets.

Burra shashidher et al., 2012, formulated and evaluated carvedilol liquisolid tablets. A novel powder solution technology involves absorption and adsorption efficiency, which makes use of liquid medications, admixed with suitable carriers, coating materials and formulated into a free flowing, dry looking, non-adherent and compressible powder forms. The crystalline state of drug is changed to amorphous state due to liquisolid formation and is confirmed by both DSC and X-ray diffraction results. The amorphous form exhibited increased wetting properties because of subsequent increased surface area of the particle size.

Shah C.V.et al., 2012, designed, developed and optimized valsartan liquisolid tablets using Box – Behnken design. This study was designed to optimize and evaluate the effects of different formulation variables. Amount of liquid (X1),ratio of carrier to coating material (X2) and amount of magnesium oxide (X3) on angle of repose (Y1), hardness (Y2) and invitro release (Y3) of formulation using three level Box –Behnken stastical design. The non–linear quadratic model generated by the design in the form of Y=A0 + A1X1 + A2X2 + A3X3 + A4X1X2 + A5X2X3 + A6X1X3 + A7X12 + A8X22 + A9X32 + E, where y is the measured response surface plots were depicted based on the equation given by the model.

Dnyanesh walunj et al., 2012, formulated and evaluated tamoxifen citrate liquisolid compacts were prepared using a mathematical model to calculate the requiredquantities of powder and liquid ingredients to produce acceptably flowable andcompressible admixture. Avicel PH 102, Aerosil 200, croscarmellose sodium andpropylene glycol were employed as carrier, coating material, disintegrant and nonvolatile solvent respectively for preparing liquisolid compact. This study was concluded that liquisolid technique is a promising alternative for improvement of dissolution property of water insoluble drugs.

Sateesh kumar Vemula et al., 2012, enhanced dissolution rate of nimesulide byliquisolid technique. Liquisolid tablets were prepared by using polyethylene glycol 400 as a non-volatile liquid vehicle, microcrystalline cellulose, hydroxyl propyl methyl cellulose E-15, starch were used as carrier materials and silica gel as coating material in different ratios. *Invitro* dissolution profiles of liquisolid formulations were studied and compared with conventional formulation in pH7.4 phosphate buffer and it was found that

liquisolid tablets formulated with microcrystalline cellulose showed significant higher drug release rates than conventional tablets due to increase in wetting properties.

Sidharth patil et al., 2012, formulated and evaluated liquisolid tablets of non steroidal anti inflammatory drug ibuprofen were prepared by using microcrystalline cellulose (Avicel PH 101) as a carrier material, silica gel as coating material, poly ethylene glycol 400 as non – volatile water miscible liquid vehicle and 5%sodium starch glycolate used as super disintegrating agent. The results showed that liquisolid formulations of ibuprofen exhibited higher percentage of drug release than marketed formulation.

Kamalakannan V. et al., 2012, formulated and evaluated tinidazole liquisolid tablets. A liquisolid system is formed by converting a liquisolid formulation into a dry, free-flowing and compressible powder mixture with selected carrier material and coating material. Liquisolid tablet formulation by using 20:1 ratio of powder excipients ratio (480mg of Avicel and 24mg of Cab-O-sil) and 100% w/w tinidazole in PG 600 solvent were satisfying the requirements.

Sirisha V.N.L. et al., 2012, prepared and evaluated (*in vitro*) liquisolid compacts of glibenclamide. Liquisolid tablets were prepared by using PEG 400 as non- volatile liquid vehicles and Avicel PH 101, Aerosil as carrier and coating materials respectively. The properties of glibenclamide particles were changed by dispersing the drug particles in a non–volatile liquid vehicle, which in turn increases the wetting properties and surface area of drug particles, and hence improve the dissolution profiles and oral bioavailability of the drug.

Lakshmi P.K. et al., 2011, prepared and comparatively evaluated liquisolid compacts and solid dispersions of valsartan. Liquisolid technology and solid dispersion by kneading method used to improve the solubility of the drug by using non-volatilesolvents. Various non-volatile solvents were used such as PG, PEG and glycerin. The carrier and coating material play an important role in improving the solubility of the drug. Solid dispersion by kneading method is another attempt to improve solubility. Various carrier materials were used such as PVP K30, PEG 6000 and mannitol. These carriers were used in various ratios to improve its solubility. The results concluded that the liquisolid compacts enhanced the solubility of valsartan in comparison to traditional solid dispersion method.

Vijayakumar Nagabandi et al., 2011, formulated, developed and evaluated liquisolid systems to improve the dissolution rate of ketoprofen using different carrier materials such as microcrystalline cellulose (Avicel PH101), starch, dicalcium phosphate, lactose and silica gel as coating material. Polyethylene glycol 400 was used as non-volatile water miscible liquid vehicle. The ratio of carrier to coating material was kept constant in all formulations of ketoprofen which exhibited higher percentage of drug release than marketed formulation.

Vijayakumar Nagabandi et al., 2011, formulated, developed and evaluated liquisolid systems to improve the dissolution rate of naproxen with two different liquid vehicles, namely polyethylene glycol 400 and propylene glycol. Two different carrier materials were used namely microcrystalline cellulose (Avicel PH101) and dicalcium phosphate. Silica gel as coating material and sodium starch glycolate as disintegrating

agent in all formulations. The results showed that liquisolid formulations of ketoprofen exhibited higher percentage of drug release than marketed formulation.

Ali Nokhodchi et al., 2010, studied the effect of co solvent and HPMC on theophylline release. Liquisolid tablets were prepared by mixing liquid medication with silica. Eudragit RL or RS followed by the compaction of the mixture. For comparison purposes physical mixtures of all ingredients were prepared. The effect of liquid medication and HPMC concentration on drug release was investigated. The sustained release action of HPMC was enhanced in liquisolid compacts in comparison to simple sustained release matrix tablets.

Amal A. Elkordy et al., 2010, developed liquisolid systems to improve the dissolution rate of furosemide were prepared using microcrystalline cellulose (AvicelPH101)as carrier and fumed silica (Cab-O-sil M-5) as coating material. Polyethylenepolyoxypropylene- polyoxyethylene block copolymer (Synperonic PE/L81) 1, 2, 3 propranolol, homopolymer, (a2) 9-octadecenoate (caprol PGE-860) and polyethylene glycol 400 (PEG 400) were used as non-volatile water miscible liquid vehicles. The results showed that all formulations exhibited higher percentage of drug dissolved in water (pH6.4-6.6) compared to that of acidic medium (pH1.2). Liquisolid compacts containing synperonic PE/L81 showed higher release rate at different pH values. Formulations with PEG 400 displayed lower drug release rate compared to conventional tablet.

Amrit B. Karmarkar et el., 2010, evaluated (*in vitro*) dissolution profile comparisonmethods of sustained release tramadol hydrochloride with marketed sustained release tablets. Liquisolid sustained release formulations were prepared by

using HPMC K4M as a sustained release agent. Liquisolid compacts were evaluated .The dissolution profile followed the Peppas model as “best fit”. Two-way ANOVA results revealed a significant difference in dissolution profiles. This systematic approach to producing a formulation was found to help with analyzing the sustained release of tramadol hydrochloride.

Dinesh M. Pardhi et al., 2010, developed liquisolid technique for enhancement of dissolution properties of carvedilol. The invitro release pattern of liquisolid compacts and directly compressed tablets were studied using USP-2 apparatus. From this study it concludes that the liquisolid technique is a promising alternative for improvement of dissolution property of water insoluble drugs.

Khalid M. El-Say et al., 2010, formulated and evaluated rofecoxib liquisolid tablets.The effect of powder substrate composition on the flow ability and compressibility of liquisolid compact were evaluated specifically several liquisolid formulation containing 25mg rofecoxib using different carrier to coating ratios in their powder substrates and fixed liquid medication were prepared. From the previous results, it was concluded that addition of 10 % Cab-O-Sil and 5% magnesium oxide improved both the flow ability and compressibility of tested rofecoxib powders. These two substances change the flow ability from bad flow to satisfactory flow. The prepared liquisolid tablets showed higher dissolution profile than the three studied commercial tablet.

Shashibher Burra et al., 2010, enhanced the solubility and dissolution rate of furosemide through liquisolid technique. The drug dissolution was tested using different dissolution media such as 1.2pH, 5.4pH, 6.8pH, 7.4pH. The results showed that liquid

solid tablets have higher drug dissolution rates than the conventional and directly compressible tablet

Sanjeev raghavendra Gubbi et al., 2010, formulated and characterized atorvastatin calcium liquisolid compact were prepared using a mathematical model for calculating required quantities of powder and liquid ingredients to produce an acceptably flowable and compress able admixture. Avicel PH102, Aerosil 200 and Explotab were employed as carrier, coating material and disintegrant respectively. This study shows that the liquisolid technique is a promising alternative for improvement of the dissolution rate and oral bioavailability of water insoluble drugs confirmed by estimating the pharmacokinetic parameters *in vivo* in rabbits.

Amrit B. Karmarkar et al., 2009, enhanced dissolution rate of fenofibrate using liquisolid tablet technique. Liquid medications such as solutions or suspensions of water insoluble drugs in suitable non-volatile liquid vehicles can be easily converted into powders with acceptable flow properties and compression behavior by using powder excipients. Enhanced drug release profiles due to increased wetting properties and surface of drug available for dissolution was obtained in case of liquisolid tablets.

Amal A. Elkordy et al., 2009, formulated and evaluated the effects of liquisolid formulations on dissolution of naproxen with three different liquid vehicles namely cremophor EL, synperonic PE/L61 and polyethylene glycol 400 at two drug concentrations 20% w/w and 40% w/w. Avicel PH102 was used as a carrier material, Cab-O-sil M5 as a coating material, maize starch as a disintegrant. Liquisolid tablets formulated with cremophor EL at drug concentration of 20% w/w produced high dissolution profile with acceptable tablet properties.

Sanjeev Gubbi et al., 2009, performed liquisolid technique for enhancement of dissolution properties of bromhexine hydrochloride. Different LS compacts were prepared using a mathematical model to calculate the required quantities of powder and liquid ingredients to produce acceptably flowable and compressible mixture. The prepared LS compacts were evaluated. From this study it was concluded that the LS technique is a promising alternative improvement of dissolution property for water insoluble drugs.

Yadav V.B. et al., 2009, improved solubility and dissolution of indomethacin by liquisolid compaction and granulation technique. In the liquisolid system IM was dispersed on polyethylene glycol 400(PEG 400) as a non-volatile liquid vehicle. Microcrystalline cellulose (Avicel PH102) and dibasic calcium phosphate (DCP) were used as a carrier; hydroxypropyl methyl cellulose (HPMC) as coating material and sodium starch glycolate (SSG), croscarmellose sodium (CCS) were used as disintegrants. It was observed that the drug release rate, water solubility and wettability of liquisolid granules containing super disintegrants were on higher side compared to liquisolid granules without super disintegrants.

Ali Nokhodchi et al., 2008, carried out liquisolid technique as a new approach to sustain propranolol hydrochloride release from tablet matrices. The drug was dispersed in polysorbate 80 as liquid vehicle. Then the binary mixture of eudragit RL or RS (carrier) and silica (coating material) was added to the liquid medication under continuous mixing in a mortar. The final mixture was compressed using a manual tableting machine. The release rate of propranolol HCl from liquisolid compacts was compared with that of conventional tablets. The drug prepared by liquisolid technique

showed greater retardation properties in comparison with conventional tablets. This investigation provided evidence that polysorbate 80 (Tween 80) has important role insustaining the release of drug from liquisolid matrices.

Ali Nokhodchi et al., 2007, studied liquisolid technique as a tool for enhancement of poor water soluble drugs and evaluated their physiochemical properties. Different formulations of liquisolid tablets, using different co-solvents, (non-volatile solvents) were prepared and the effect of aging on the dissolution behavior of indomethacin liquisolid compacts was investigated. Dissolution test was carried out at two different pH, 1.2 and 7.2 to simulate the stomach or intestine fluid respectively. Liquisolid compacts containing propylene glycol as vehicle produced higher dissolution rates in comparison with liquisolid compacts containing PEG 400 or Tween 80 of the same concentration.

Ali Nokhodchi et al., 2007, enhanced the dissolution rate of high dose water insoluble drug (carbamazepine) using liquisolid technique. Different liquisolid formulations of drug were accomplished by dissolving the drug in the non–toxic hydrophilic liquids and adsorbing dissolution on to the surface of silica. In order to reduce the amounts of carrier and Aerosil in liquisolid formulations some additives namely polyvinyl pyrolidone (PVP), hydroxypropyl methyl cellulose (HPMC) and polyethylene glycol (PEG 35000) were added to liquid medication to increase loading factor. The effects of various ratios of carrier to coating material, PVP concentration,effect of aging and type of carrier on dissolution rate of liquisolid compacts were studied. The results showed that drug loading factors was increased significantly in the presence of additives. It was shown that microcrystalline cellulose

had more liquid retention potential in comparison with lactose and the formulations containing microcrystalline cellulose as carrier, showed higher dissolution rate. by decreasing the ratio of microcrystalline cellulose to silica from 20 to 10, an improvement in dissolution rate was observed.

Dina Louis et al., 2007, improved the dissolution properties of carbamazepine through application of liquisolid tablet technique. Avicel PH 102 and Aerosil 200 were used as carrier and coating material respectively and Explotab was used as disintegrant to prepare four tablet formulae, out of which formula 1 was successfully compressed into tablets. The prepared tablets showed good wettability, rapid disintegration and acceptable dissolution rate comparable to the generic product.

Nokhodchi A. et al., 2005, enhanced the dissolution rate of piroxicam using liquisolid compacts. The dissolution behavior of drug from liquisolid compacts was investigated in simulated gastric fluid (SGF pH1.2) and simulated intestinal fluid (SIF pH7.2). The results showed that liquisolid compacts demonstrated significantly higher drug release rates than those of conventionally made. This was due to an increase in wetting properties and surface of drug available for dissolution.

Khaled A. Khaled et al., 2001, evaluated (*in vivo*) hydrochlorothiazide liquisolid tablets in beagle dogs. The drug was administered orally as a single 25mg dose of commercial and liquisolid tablets on two occasions in a randomized two-way cross over design. The absolute bioavailability of the drug from the liquisolid tablets was 15% higher than that from the commercial one. The parametric 90% confidence intervals for the different parameters were higher than the commonly expected intervals for bioequivalency, indicating greater bioavailability of the liquisolid tablets.

Spiro Spireas et al., 1998, enhanced prednisolone dissolution properties using liquisolid compacts. According to the new formulation method of liquisolid compacts, liquid medications such as solutions or suspensions of water insoluble drugs in suitable non – volatile liquid vehicles can be converted into acceptably flowing and compressible powders by blending with selected powder excipients. Liquisolid compacts demonstrated significantly higher drug release rates, in different dissolution media and volumes, compared to tablets prepared by the direct compression method.

CHAPTER-3

AIM OF THE WORK

CHAPTER-III

AIM OF THE WORK

The poor dissolution rate of water insoluble drug is a major impediment to the development of pharmaceutical dosage forms. The oral absorption of drug is most often controlled by dissolution in the gastrointestinal tract. Different methods are employed to improve the dissolution characteristics of poorly water soluble drugs, like solubilization, pH adjustment, co-solvents, microemulsion, particle size reduction, use of surfactant as a solubilizing agent, prodrug approach etc. Amongst these the most promising method for promoting dissolution is the use of the liquisolid system.

Liquisolid system refers to formulation by con version of oily liquid drug and solutions or suspensions of water insoluble solid drugs in non-volatile solvents into dry, non-adherent, free flowing and compressible powder mixtures by blending the suspension or solution with selected carrier and coating materials.

Pioglitazone is an orally-active thiazolidinedione with antidiabetic properties and potential antineoplastic activity. Pioglitazone activates peroxisome proliferator- activated receptor gamma (PPAR-gamma), a ligand- activated transcription factor, thereby inducing cell differentiation and inhibiting cell growth and angiogenesis. This agent also modulates the transcription of insulin- responsive genes, inhibits macrophage and monocyte activation and stimulates adipocyte differentiation.

Pioglitazone is a class II drug of BCS classification; hence it has a low solubility and low permeability. Due to the low solubility it has a low oral bioavailability

To overcome the drawbacks, various techniques are employed to enhance the dissolution of water insoluble drug. Among these the “liquisolid” is a newly developed technique. As the drug is in the form of liquid medication, it is in either solubilized or molecularly dispersed state. Due to increased wetting and surface area for dissolution, liquisolid tablets of water insoluble drugs may show improved dissolution properties and in turn increases bioavailability.

The aim of present study is to formulate liquisolid tablets of Pioglitazone using different non-volatile liquid (Propylene glycol, Polyethylene glycol-400 and Tween 80), Avicel PH102 as a carrier and Aerosil 200 as a coating material. The best formulation selection is on the basis of release pattern and is to be compared with directly compressed tablet and pure drug.

CHAPTER-4

PLAN OF WORK

CHAPTER - IV

PLAN OF WORK

1.PREPARATION OF STANDARD CALIBRATION CURVE

a)Determination of λ max

b)Preparation of calibration curve

2.SOLUBILITY STUDIES

3.PREFORMULATION (COMPATIBILITY) STUDIES

a) Infrared spectroscopic studies

4.FLOWABLE LIQUID-RETENTION POTENTIAL (Φ-VALUE) OF EXCIPIENTS

a) Determination of the angle of slide

b) Determination of flowable liquid-retention potential (ϕ-value)

5.PROCEDURE FOR PREPARATION OF LIQUISOLID POWDER

6.PREPARATION OF DIRECTLY COMPRESSED TABLETS

7.PRECOMPRESSIONAL EVALUATION OF POWDER BLEND

a) Angle of repose

b) Bulk Density

c) Tapped Density

d) Carr's Index

e) Hausner's Ratio

f) Drug content for Powder Blend

8.POSTCOMPRESSIONAL EVALUATION OF LIQUISOLID TABLETS

a) General appearance

b) Thickness

c) Hardness

d) Weight variation

e) Friability test

f) Estimation of drug content

g) Disintegration test

***9. IN VITRO* RELEASE STUDIES**

10. POWDER X-RAY DIFFRACTION STUDIES

11. ASSESSMENT AND COMPARISON OF DRUG DISSOLUTION RATES

12. SELECTION AND EVALUATION OF BEST FORMULATION

a) Comparison of dissolution studies of best formulation with pure drug and directly compressed tablets

b) Infrared spectroscopic studies for best formulation

c) Differential scanning colorimetric (DSC) studies for best formulation

d) Drug release kinetics studies

e) Stability studies

CHAPTER-5

MATERIALS AND EQUIPMENTS

MATERIALS AND EQUIPMENTS

MATERIALS	DISTRIBUTORS
Pioglitazone.HCL	Madras pharma,Chennai.
Propylene glycol	Pharmafabrikon ,Madurai.
Polyethylene glycol 400	Pharmafabrikon ,Madurai.
Tween 80	Universal scientific appliances,Madurai.
Microcrystalline cellulose	Madras Pharma,Chennai.
Aerosil 200 (silica)	Micro labs Ltd.Bangalore.
Crospovidone	Ordain health care,Chegalpet
Magnisum stearate	Madras Pharma,Chennai.
Talc	Ordain health care.Chennai.
Methanol	Universal scientific appliances, Madurai.

EQUIPMENTS	SUPPLIERS
Electronic Weighing Balance	A & D Company,Japan.
Multi punch tablet compression machine	Fluid Pack, Ahmedabad
UV Visible spectrophotometer	Shimazdu UV-1700,Japan
Digital tablet dissolution test apparatus	Lab India Disso Apparatus 2000, India.
Friability test apparatus	Indian Equipment corporation,Mumbai.
Tablet hardness tester	Scientific Equipment Corporation,Mumbai
Digital Vernier caliper	Linker ,Mumbai.
Disintegration test apparatus	Rolex ,India.
Fourier transform infrared spectroscopy	Shimadzu , Japan.
Differential scanning colorimeter	DSC Q200 V24.4 Instrument,USA.
Power X-ray diffractometer	XD,Shimadzu,Japan.
Scanning electron microscopy	Hitachi X650,Tokyo,Japan.
Magnetic stirrer	M.C.Dalal,Chennai.
Mechanical shaker	Secor ,India
Stability Chamber	In labs Equipments (P) Ltd.Madras.
Hot air oven	Industrial Headans, Chennai.

CHAPTER-6

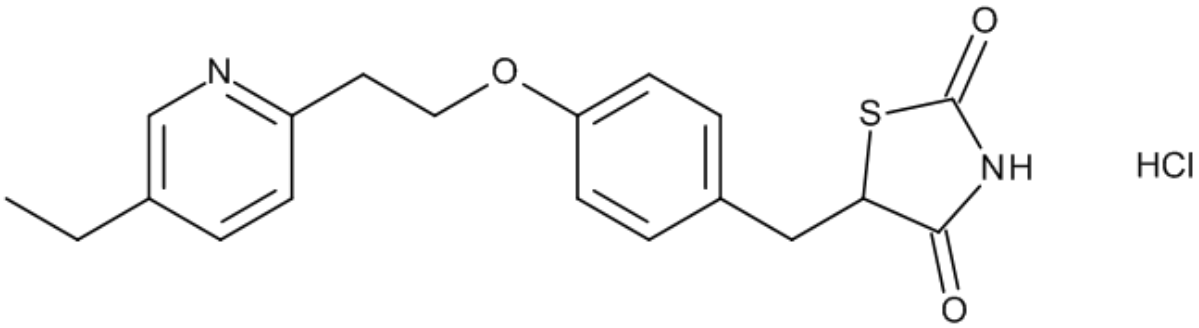
DRUG PROFILE

CHAPTER-VI

DRUG PROFILE

DRUG NAME **:** PIOGLITAZONE.HCL

STRUCTURAL FORMULA:



CHEMICAL FORMULA:

$C_{19}H_{20}N_2O_3S.HCL$

CHEMICAL NAME:

5-({4-[2-(5-ethylpyridin-2-yl)ethoxy]phenyl}methyl) 1,3-thiazolidine-2,4-dione]

MOLECULAR WEIGHT **:** 356.44gm/mol

DESCRIPTION

Physical state	:	Solid
Colour	:	White to off white
Solubility	:	Soluble in Methanol , N,N-dimethylacetamide, Acetic acid ,Slightly solube in Ethanol, 1-propanol. Practically insoluble in water.

Molecular weight	:	356.44 g/mol
pKa	:	5.6
LogP value	:	2.3
Refractivity	:	97.71 $m^3.mol^{-1}$
Melting Point	:	183-184^{O}C
Polarizability	:	37.91

MECHANISUM OF ACTION

Pioglitazone acts as a selective agonist at Peroxisome Proliferator Activated Receptor Gamma (PPARγ) in target tissues for insulin action such as adipose tissue, skeletal muscle, and liver. Activation of PPAR-gamma receptors increases the transcription of insulin-responsive genes involved in the control of glucose production, transport, and utilization. In this way, pioglitazone both enhances tissue sensitivity to insulin and reduces the production of glucose via the liver (hepatic gluconeogenesis). Thus, insulin resistance associated with type 2 diabetes mellitus is improved without an increase in insulin secretion by pancreatic β cells.

Pioglitazone acts principally by increasing insulin sensitivity in target tissues, as well as decreasing hepatic gluconeogenesis. Pioglitazone is a peroxisome proliferator-activated receptor (PPAR) agonist that increases transcription of insulin-responsive genes and increases insulin sensitivity

PHARMACOKINETICS

Absorption

oral administration of Pioglitazone, peak concentrations of pioglitazone were observed within 2 hours. Food slightly delays the time to peak serum concentration (T max) to 3 to 4 hours, but does not alter the extent of absorption (AUC)

Volume of Distribution

Mean volume of distribution at steady-state of Pioglitazone is approximately

0.63 ± 0.41 L/Kg

Protein Binding

The plasma protein binding of recemic pioglitazone is >99%.

Metabolism

Pioglitazone is extensively metabolized by hydroxylation and oxidation; the metabolites also partly convert to glucuronide or sulfate conjugates. Metabolites M-III and M-IV are the major circulating active metabolites in humans. The cytochrome P450 isoforms involved are CYP2C8 and, to a lesser degree, CYP3A4 with additional contributions from a variety of other isoforms including the mainly extrahepatic CYP1A1

Route of elimination

oral administration, approximately 15% to 30% of the pioglitazone dose is recovered in the urine. Renal elimination of pioglitazone is negligible, and the drug is excreted primarily as metabolites and their conjugates.

Half Life

The terminal elimination half life of Pioglitazone is approximately 3-7 hours.

INDICATIONS AND USAGE

Adjunct to diet and exercise in type 2 diabetes, as monotherapy or in combination with metformin, insulin, or a sulfonylurea. Limitations of use: not for treating type 1 diabetes or diabetic ketoacidosis**.**

Adult:

≥18yrs: Without CHF: initially 15mg or 30mg once daily; max 45mg once daily. With CHF (NYHA Class I or II): initially 15mg once daily. Concomitant insulin or sulfonylurea: reduce dose of these if needed. Concomitant strong CYP2C8 inhibitors: max 15mg daily.

DOSAGE AND ADMINISTRATION

Initially, 15 or 30 mg once daily. If response is inadequate, increase dosage in increments, up to a maximum dosage of 45 mg daily.If response is inadequate with monotherapy, consider combination therapy

DOSAGE FORMS

Tablet,15mg

Tablet, 30mg

Tablet, 45mg

CONTRAINDICATIONS

- ❖ hypersensitivity to the active substance or to any of the excipients,
- ❖ cardiac failure or history of cardiac failure (NYHA stages I to IV),
- ❖ hepatic impairment,

- diabetic ketoacidosis
- current bladder cancer or a history of bladder cancer
- uninvestigated macroscopic haematuria
- Heart failure

ADVERSE REACTIONS

- Muscle pain
- Weight gain
- Sore throat
- Tooth problems
- Dark urine
- Plasma volume expension
- Yellowing of eye / skin
- Myalgia
- Headache
- Mild anaemia
- Swelling of the face

OVERDOSAGE

- Trouble breathing

DRUG INTERACTION

Beta-blocker medications (such as metoprolol,propranolol, glaucoma eye drops such as timolol) may prevent the fast/pounding heartbeat you would usually feel when your blood sugar falls too low (hypoglycemia).

Other symptoms of low blood sugar, such as dizziness, hunger, or sweating, are unaffected by these drugs.

BRAND NAMES

- Actos (Takeda Pharmaceuticals,U.S)
- Betapride (Avunash Pharmaceutical.,India)
- Diavista (Dr.Reddy's Pharmaceutical Ltd.India)
- Glizone (Zydus Pharmaceuticals Ltd. India)

CHAPTER-7

EXCIPIENTS PROFILE

CHAPTER-VII

EXCIPIENT PROFILE

PROPLENE GLYCOL

Synonyms :

- 1,2-Dihydroxypropane
- 2-hydroxypropanol
- Methyl ethylene glycol
- Methyl glycol
- Propane-1,2-diol

Chemical name:

- 1,2-propanediol

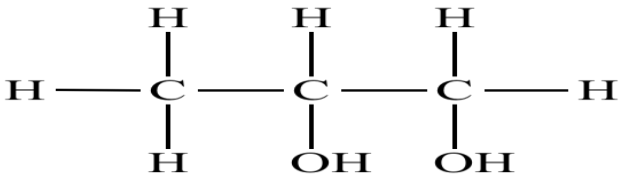
Empirical formula:

- $C_3H_8O_2$

Molecular weight:

- 76.09

Structural formula:



Functional category:

- Antimicrobial preservative
- Plasticizer
- Water –miscible cosolvent
- Stabilizer for vitamins
- Disinfectant
- Humectants

HLB value:

- 11.6

Viscosity at 25 ^{0}C

- 58.1mPa s

Application in pharmaceutical formulation:

- Propylene glycol has become widely used as a solvent , extractant and preservative in a variety of parenteral and nonparenteral pharmaceutical formulations.
- Propylene glycol is commonly used as a plasticizer in aqueous film-coating formulations.
- Propylene glycol is also used in cosmetics and in the food industry as a carrier for emulsifiers and as a vehicles for flavors in preference to ethanol, since its lack of volatility provides a more uniform flavor.

Description:

- Propylene glycol is a clear, colorless, viscous, practically odourless liquid with a sweet acrid taste resembling that of glycerin.

Melting Point:

- -59^0C

Solubility:

- Soluble in acetone, chloroform, ethanol, glycerin and water.

Stability and storage condition:

- Propylene glycol is chemically stable when ethanol (95%), glycerin, or water
- Propylene glycol is hygroscopic and should be stored in a well-closed container, protected from light ,in a cool ,dry place.

Incompatibilities:

- Propylene glycol is incompatible with oxidizing reagents such as potassium permanganate.

Handling Precaution:

- Propylene glycol should be handled in a well-ventilated environment, eye protection is recommended.

  (Hand book of pharmaceutical Excipient by Raymond C Rowe.,5^{th} Edition)

POLYETHYLENE GLYCOL 400

Synonyms:

- Carbowax Sentry
- Lutrol E
- Pluriol E
- Lipoxol

Chemical name:

- Polyethylene glycol 400

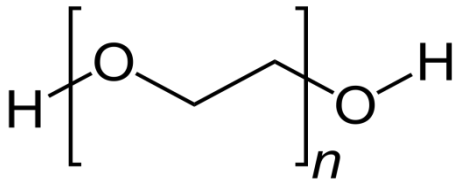
Empirical formula:

- $H(OCH_2CH_2)_nOH$

Molecular weight:

- 400 (380-400) g/mole

Structural formula:



Functional category:

- Ointment base
- Plasticizer
- Suppository base
- Tablet and Capsule lubricant

HLB value:

- 11.6

Viscosity at 25 ^{0}C

- 105-130 mPas

Application in pharmaceutical formulation:

- Polyethylene glycol is widely used in parenteral , topical, ophthalmic and oral preparations.

Description:

- Clear liquid, odourless

Melting Point:

- 4^0C (39.2^OF)

Solubility:

- Soluble in cold water, hot water, Slightly soluble in aliphatic hydrocarbons. Readily soluble in aromatic hydrocarbons.

Stability:

- Stable under ordinary condition hygroscopic.

Storage:

- Tightly closed container. Keep container in a cool, well-ventilated area.

Precautions:

- Keep away from heat, source of ignition and incompatibles such as oxidizing agents, acids, alkalis.
- Wear suitable protective clothing.

(www.chemicalland.com and Hand book of Pharmaceutical Excipients by Raymond C Rowe.,5th Edition)

TWEEN 80

Synonyms:

- Armotan PMO 20
- Capmul POE-0
- Cremophor Ps 80
- Montanox 80

Chemical name:

- Polyoxyethylene 20 sorbitan monoleate

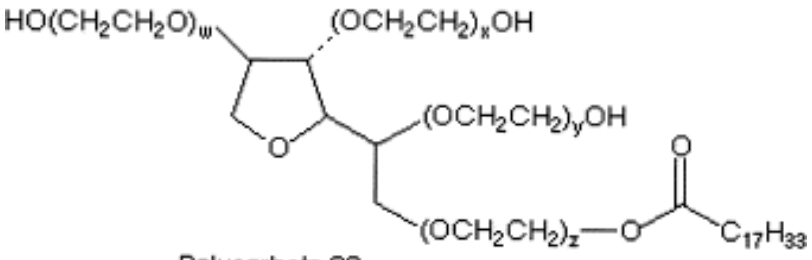
Empirical formula:

- $C_{64}\ H_{124}\ O_{26}$

Molecular weight:

- 1310

Structural formula:



Polysorbate 80
(Sum of w, x, y, and z is 20)

Molecular Mass = 1310

HLB value:

- 15

Functional category:

- Emulsifying agent
- Non-ionic surfactant
- Solubilizing agent
- Wetting agent
- Dispersing / suspending agent

Viscosity at 25^{0}C:

- 425 mPas

Application in pharmaceutical formulation:

- They may be used as solubilizing agents for a variety of substances including essential oils and oil-soluble vitamins and as wetting agents in the formulation of oral and parenteral suspentions.

- They have been found to be useful in improving the oral bioavailability of drug molecules.

- Polysorbates are also widely used in cosmetics and food products.

Description:

- Yellow oily liquid

Melting point:

- -20.556^{0}C(-5)

Solubility:

- Soluble in methanol. Easily soluble in cold water .hot water .soluble in toluene ,alcohol .cottonseed oil. Ethyl acetate

- Insoluble in mineral oil.

Stability and storage condition:

- Polysorbates are stable to electrolytes and weak acids and bases.

- Polysorbate should be stored in a well-closed container. Protected from light it should be stored in a cool. dry place.

Incompatibilities:

- The antimicrobial activity of paraben preservatives is reduced in the presence of polysorbates.

Handling Precaution:

- observe normal precautions appropriate to the circumstances and quality of material handled eye protection and gloves are recommended.
  (Hand book of pharmaceutical Excipient by Raymond C Rowe..5th Edition)

MICROCRYSTALLINE CELLULOSE

Synonyms :

- Avicel PH
- Crystalline cellulose
- Cellet
- Emcocel
- Hellulosum microcristalinum

Chemical name:

- Cellulose

Empirical formula:

- $(C_6H_{10}O_5)_n$

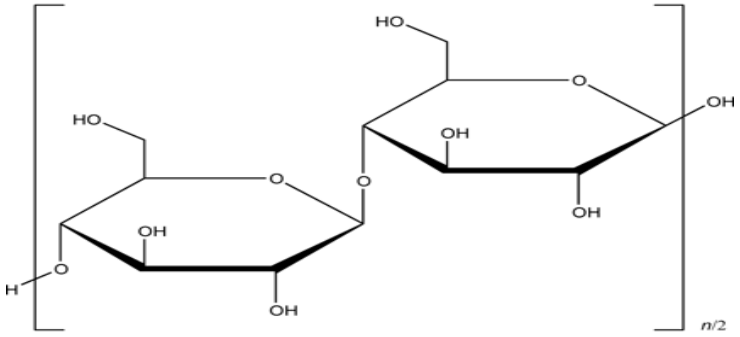
Molecular weight:

- 36000 gm/mol

Functional category:

- Adsorbent
- Suspending agent
- Tablet and capsule diluents
- Tablet disintegrant

Structural formula:



Application in pharmaceutical formulation:

- Microcrystalline cellulose is widely used in pharmaceuticals. Primarily used as binder / diluents in oral tablets and capsule formulation.
- Micerocrystalline cellulose is also used in cosmetics and food products.

Description :

- Microcrystalline cellulose is a white, odourless, tasteless, crystalline powder composed of porous particles.

Melting Point:

- 260-270^{0}C

Solubility :

- Slightly soluble in 5% w/v NaOH solution ,practically insoluble in water and most organic solvents.

Solubility and storage condition:

- Microcrystalline cellulose is stable though hygroscopic material.
- It should be stored in a well-closed container in a cool, dry place.

Incompatibilities:

- Microcrystalline cellulose is incompatible with strong oxidizing agent.

Handling Precautions:

- Microcrystalline cellulose may be irritant to the eyes, Gloves, eye protection and dust mask are recommended.

(Hand book of pharmaceutical Excipient by Raymond C Rowe.,5th Edition)

SILICA

Synonyms:

- Aerosil
- Cab-O-sil
- Colloidal silica
- Fumed silica
- Fumed silicon dioxide
- Silicone dioxide colloidal

Chemical name:

- Silicon dioxide

Empirical formula:

- SiO_2

Molecular weight:

- 60. 08

Functional category:

- Adsorbent
- Anticaking agent
- Glidant and Tablet disintegrant
- Emulsion stabilizer
- Viscosity increasing agent

Application in pharmaceutical formulation:

- It is improves the flow properties of the dry powders.
- It is used as an adsorbent dispersing agent for liquids in powders.
- Eliminate hard settling and minimize the clogging of spray nozzle

Description:

- Colloidal silicone dioxide is a light, loose, bluish-white coloured, tasteless, odourless and amorphous powder**.**

Melting Point:

- 1600^{o}C

Solubility:

- Soluble in hot solution of alkali hydroxide. Practically insoluble in water, organic solvents and acids.

Storage condition:

- It should be stored in a well closed container.

Incompatibilities:

- It is incompatibility with diethylstilbesterol preparations.

Handling Precautions:

- A dust mask should be used, when handling small quantity. For large quantities, a dust respirator is recommended.

(www.chemicallab.com and Hand book of pharmaceutical Excipient by Raymond C Rowe., 5th Edition)

CROSPOVIDONE

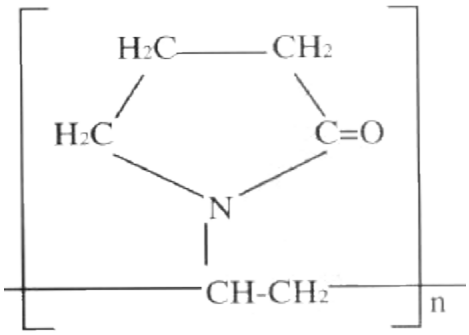
Synonym:

- Cross linked povidone
- Kollido
- 1-vinyl-2-pyrrolidone homopolymer
- Polyplasdone
- Polyvinylpolypyrrolidone

Chemical name :

- 1-Ethylene-2-pyrrolidinone homopolymer

Functional formula :



Empirical formula:

- $(C_6H_9NO)_n$

Molecular weight:

- >1000 000

Functional category:

- Tablet disintegrant.

Application in pharmaceutical formulation:

- Tablet disintergrant and dissolution agent.
- Solubility enhancer for poorly soluble drug

Description:

- Crospovidone is a white-creamy white
- Free flowing
- Practically tasteless
- Hygroscopic powder

Melting Point:

- $150^{O}C$

Stability and Storage condition:

- Crospovidone is hygroscopic
- It should be stored in an airtight container in a cool, dry place.

Incompatibilities:

- Crospovidone is compatible with most organic and inorganic pharmaceutical ingredients.
- When exposed to a high water level .
- Crospovidone may form molecular adduct with some materials.

Handling Precautions:

- Observe normal precaution appropriate to the circumstances and quantity of material handled.
- Eye protection gloves and a dust mask are recommended

  (Hand book of Pharmaceutical Excipients by Raymond C Rowe 5th Edition.)

TALC

Synonym:

- Altalc
- Hydrous magnesium calcium silicate
- Hydrous magnesium silicate

Chemical name:

- Talc
- Purified talc
- Talcum

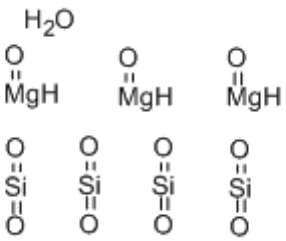
Empirical Formula:

- Talc is purified, hydrated, magnesium silicate.
- Mg6 ((Si2O5)4(OH) 4)
- It may contain small variable amounts of silicate and iron.

Molecular weight:

- 379.27

Structural Formula:



Functional Category :

- Anticaking agent
- Glidant
- Diluent
- Lubricant

Application in pharmaceutical formulation:

- Talc is widely used in solid dosage formulations.
- Lubricant and Glidant. (1.0-10.0)
- Diluents in tablet and capsule. (5.0-30)
- It is widely used as a dissolution retardant in the development of controlled-release products.
- Talc is novel powder coating for extended release pellets and as an adsorbent.
- It is used as a dusting powder. (concentration 90.0-99.0)
- It is used to clarify liquids and is used in cosmetics and food products.
- It is used in baby powder.

Description:

- Talc is very fine, white to grey-white, odourless, impalpable, unctuous, crystalline powder. It adheres readily to the skin and is soft to touch and free from grittiness.

Melting Point:

- 800^{o}C

Solubility:

- Practically insoluble in organic solvent, water and in dilute acids & alkalis.

Stability and Storage condition:

- Talc is a stable material and may be sterilized by heating at 160^{o}C for not less than one hour.
- It may also be sterilized by exposure to ethylene oxide or gamma radiation.
- Talc should be stored in well closed container in a cool, dry place.

Incompatibilities:

- Incompatible with quaternary ammonium compounds.

Handling Precautions:

- Talc is irritant if inhaled and prolonged exposure may cause pneumoconiosis.
- In the UK, the occupational exposure limit for talc is long-term (8 hour TWA). Eye protection, gloves and respirator are recommended.

(Hand book of Pharmaceutical Excipients by Raymond C Rowe.,5th Edition)

MAGNESIUM STEARATE

Synonym:

- Magnesium octadecanoate
- Octadecanoic acid
- Magnesium salt
- Stearic acid
- Magnesium salt

Chemical Name:

- Octadecanoic acid magnesium salt (557-04-0)

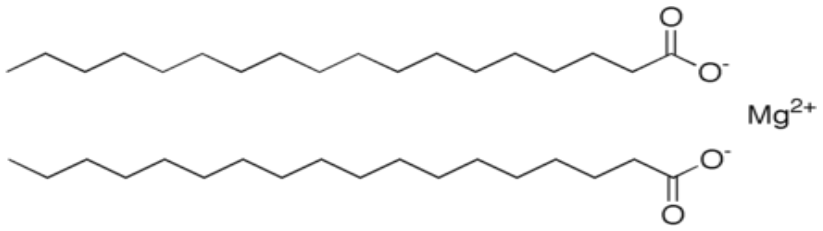
Empirical Formula:

- Magnesium stearate as a compound of magnesium with a mixture of solid organic acids that consists of variable proportions of magnesium stearate and magnesium palmitate.
- Magnesium stearate : $C_{36}H_{20}MgO_4$
- Magnesium palmitate : $C_{32}H_{62}MgO_4$

Molecular weight:

- 591.34

Structural Formula:



Functional Category:

- Tablet and capsule lubricant.

Application in pharmaceutical Formulation:

- It is widely used in cosmetics, foods and pharmaceutical formulations.
- It is used as a lubricant in capsule and tablet manufacture at concentrations 0.25% and 5.0% w/w.

Description :

- Magnesium Stearate is a very fine, light white, precipitated or milled, impalpable

  powder of low density, having a faint odour of stearic acid and a characteristic taste.

- The powder is greasy to touch and readily adheres to the skin

Melting Point:

- 117-150^{O}C

Solubility:

- Slightly soluble in warm benzene and warm ethanol.
- Practically insoluble in ethanol and water.

Stability and Storage condition:

- Magnesium stearate is stable and should be stored in well closed container in a cool, dry place.

Incompatibilities:

- Incompatible with strong acids, alkalis and iron salts.
- Magnesium stearate cannot be used with aspirin, some vitamin and most alkaloidal salts.

Handling Precautions:

- Eye protection and gloves are recommended.
- Excessive inhalation of magnesium stearate dust may cause upper respiratory tract discomfort, coughing and choking.

  (Hand book of Pharmaceutical Excipients by Raymond C Rowe.,5thEdition).

CHAPTER-8

EXPERIMENTAL PROTOCOL

CHAPTER –VIII

EXPERIMENTAL DETAILS

1.PREPARATION OF STANDARD CALIBRATION CURVE

a) Determination of λ max

Pioglitazone hydrochloride (10mg) was weighed accurately and transferred in 10 ml volumetric flask. It was dissolved in methanol and filtered it. Then filtered solution diluted up to mark with phosphate buffer (pH 7.4). The final solution contained 1000 µg of Pioglitazone per ml of the solution. The solution (1ml) was diluted further to 10 ml with the same solvent. The final solution contained 100 µg of pioglitazone per ml of the solution as a stock solution. The resultant solution is scanned in the range of (200-400nm) by Ultra visible Spectrophotometer (UV-1700 Shimadzu corporation, Japan) to get absorption maximum (λ max) (Pragati Shakya* and Kuldeep Singh., 2010)

b) Preparation of Calibration curve

From the above prepared stock solution, different concentration (5 to 25µg/ml) solutions are prepared using distilled water. The absorbances of these solutions are measured at λmax (234nm) by UV- spectrophotometer (UV-1700 Shimadzu Corporation, Japan). A standard curve is plotted using concentration on X axis and the absorbance obtained on Y-axis.

2. SOLUBILITY STUDIES :

For the selection of best non volatile solvents solubility studies are used, in this procedure, pure drug was dissolved in different non volatile solvents (propylene glycol,

Tween 80 and polyethylene glycol 400) and distilled water. Excess amount of pure drug was adding to the above solvents. From this obtained saturation solution were shaking on the rotary shaker for 48 hours at 25^0C under constant vibration. After this period the solutions are filtered, diluted and analysed by UV Spectrophotometer. Three determinations are carried out for each sample to calculate the solubility of Pioglitazone hydrochloride (Jyothi Penta et.al., 2014)

3.PREFORMULATION (COMPATIBILITY) STUDIES :

The compatibility studies are carried out by Infrared spectroscopy (IR) in order to evaluate the drug polymer interaction.

a) Fourier Transform Infrared Spectroscopic studies (FTIR):

FTIR spectroscopy helps to determine any chemical interaction between drug and excipients used in the formulation. FTIR spectra of pure Pioglitazone and physical mixtures were obtained using Shimadzu, Japan. Samples are prepared in KBr disks (2mg sample in 200mg KBr).spectrophotometer in the range of 4000-400 cm^{-1}

(J.Padmapreetha et al.,2016)

4. FLOWABLE LIQUID-RETENTION POTENTIAL (Φ-VALUE) OF THE EXCIPIENTS (AVICEL PH 102 AND AEROSIL 200)

a) Determination of the angle of slide

The angle of slide carrier and coating material (10 gm of Avicel PH 102 and Aerosil 200) is measured as follows .

Determination of the angle of the slide is done by weighing the required amount of carrier material and placed at one end of a metal plate with a polished surface. The end is radually raised till the plate becomes angular to the horizontal at which powder is about to slide. This angle is known as the angle of the slide. Angle of 33º is regarded as optimum (*Utsav et. al.2013)*

b) Determination of flowable liquid-retention potential (φ-value)

The term "flowable liquid-retential potential" (Φ-value) of a powder material describes its ability to retain a specific amount of liquid while maintaining good flow properties. The Φ-value is defined as the maximum weight of liquid that can be retained perunit weight of the powder material in order to produce an acceptably flowing liquid/powder admixture

The Φ values are calculated according to the equation

Φ value = weight of the liquid / weight of solid

The Φ-values are plotted graphically against the corresponding angles of slide (h). The Φ-value corresponding to an angle of slide of 33° represented the flowableliquid-retention potential of excipients.

The Φ-value for Avicel PH 102 and Aerosil 200 is reported in the table below and hence there is no need to determine it practically (Amal Ali Elkordy *et al*., 2013 and Dina Louis *et al*., 2008)

Table 1 : Φ–values for carrier material and coating material

(Spireas *et al*., 1998 and Abdul Hasan Sathali A. and Deepa C. *et al*., 2013)

Non volatile liquid vehicle	**Φ–values for carrier material (Avicel PH 102)**	**Φ–values for coating material (Aerosil 200)**
Propylene glycol	0.16	3.31
Poly ethylene glycol 400	0.005	3.26
Tween 80	0.003	3.95
Cremophor EL	0.18	0.80
Capryol 90	0.16	0.40

These values are used for the preparation of liquisolid tablets.

5.PROCEDURE FOR PREPARATION OF LIQUISOLID SYSTEM :

Several Pioglitazone hydrochloride liquisolid formulation are prepared in the batches of 60 tablets at ratio of (1:1) Drug : liquid vehicles. Each formulation contains avicel PH102 as carrier and aerosil 200 as coating material, at carrier /coat ratio (R value) of 5,10,15 and 20. The appropriate amounts coating material,used for each formulation depend upon Lf of that formulation. The ΦCa and ΦC0 values for each particular liquid vehicle are used to calculate Lf [Eq-(1)] of that respective liquid vehicle. Onec the liquid load factor (Lf) and amount of liquid medication (W) are determined amount of carrier (Q) and coating (q) can be calculated by rearranging Eq-(2) and (3)

$$Lf = \Phi Ca + \Phi C0 \times 1/R \quad (1)$$

$$Lf = W/Q \quad (2)$$

$$R = Q/q \quad (3)$$

The drug-vehicle liquid system is produced by mixing Pioglitazone hydrochloride (30mg/tablet) in non-volatile liquid vehicle using a mortar and pestle. To this liquid medication, the calculated amount of the carrier (Avicel PH102) is added by continuous

mixing in the mortar. Then the coating material (Aerosil 200) is carefully added and mixed until mortar contents start to look like dry powder. In the last stage of the preparation, a 5% (w/w) crospovidone as a super disintegrant and 0.75% (w/w) of magnesium stearate as a lubricant are added and mixed. All liquisolid preparations are compacted into tablets using a multi punch tablet machine (Fludi pack, Ahmedabad) having 10mm flat punch. The applied compression force is different from one formulation to another formulation depending on the weight of the tablet and the preparation (P.B.Dalvi et al.,2014, Dinesh M. Pardhi *et al*., 2010 and Spiro Spireas *et al*., 1998).

6.PREPARATION OF DIRECTLY COMPRESSED TABLETS :

For comparison conventional Pioglitazone hydrochloride (30mg/tablet) are prepared by mixing all tablet excipients, except non-volatile liquid vehicle compressed into tablets (Amal Ali Elkordy *et al*., 2012 and Spiro Spireas et *al*., 1998).

Table 2: Composition of directly compressed tablets

S.No	Ingredients	Quantity for one tablet (mg)
1.	Pioglitazone	30
2.	Tween 80	30
3.	Avicel PH 102	150
4.	Aerosil 200	15
5.	Crospovidone	11.25
6.	Magnesium stearate	1.77
7.	Talc	2.3

Total weight = 240.32mg

7. PRECOMPRESSIONAL EVALUATION OF POWDER BLEND

a) Angle of repose

The angle of repose was determined by using fixed funnel method. The powder is poured from a funnel onto a horizontal surface, it will form a cone. The angle between the sides of the cone and the horizontal is referred to as the angle of repose. The angle is a measure of the cohesiveness of the powder, as it represents the point at which the interparticle attraction exceeds the gravitational pull on a particle. A free-flowing powder will form a cone with shallow sides, and hence a low angle of repose, while a cohesive powder will form a cone with steeper sides. The angle of repose was determined by substituting the values of the base radius 'r' and height of the pile 'h' in the following equation.(Monali kalbhor et al .,2017)

$$\text{Angle of repose } (\theta) = \tan^{-1}\left(\frac{h}{r}\right)$$

Here, h = Height of pile

r = Radius of pile

θ = Angle of repose

Table 3: Limits for angle of repose

ANGLE OF REPOSE	POWDER FLOW
$<25^0$	Excellent
$25\text{-}30^0$	Good
$30\text{-}40^0$	Passable
$>40^0$	Very poor

b) Bulk density

Bulk density is the ratio between given mass of powder and its bulk volume. Bulk density is carried out in triplicate. Bulk density measurements are carried by placing fixed weight of powder in graduated cylinder and volume occupied is measured and initial bulk density is calculated. It is expressed in gm/ml. Bulk density is calculated by using following formula (Kamalakanan V. *et al*., 2012 and Pradeep Yala *et al*., 2012)

$$\text{Bulk density} = \frac{\text{Mass of the powder}}{\text{Bulk volume of the powder}}$$

c) Tapped density

Tapped density is the ratio of weight of dry powder to its tapped volume. The weighed quantity of dry powder was taken is a graduated cylinder. The cylinder was placed on the tap density tester (M/s. Inco) and subjected to 100 taps. The volume of powdered bed is measured. The tapping is continued until the difference of last two volume measurement is zero.(Srinivas Lankalapalli et. al.2014)

$$\text{Tapped density}(Dt) = \frac{\text{Weight of powder}}{\text{Tapped volume}}$$

d) Carr's Index

The Compressibility Index (Carr's Index) is a measure of the propensity of a powder to be compressed. It is determined from the bulk and tapped densities. In theory, the less compressible a material the more flowable it is. As such, it measures the relative importance of interparticulate interactions. In a free-flowing powder, such

interactions are generally less significant and the bulk and tapped densities will be closer in value.For poor flowing materials, there are frequently greater interparticle interactions, and a greater difference between the bulk and tapped densities will be observed. These differences are reflected in the Compressibility Index which is calculated using the following equation. (Manish gore et al.,2014)

$$\text{Carr's Index(CI)} = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} \times 100$$

The smaller value of the CI%,the superior the flow properties of the powder

Table 4 : Values of Carr's Index

CARR'S INDEX	TYPE OF FLOW
5-15 %	Excellent
15-25%	Good
> 25%	Poor

e) Hausner's Ratio

Hauser's ratio is an important character to determine the flow property of powder and Granules. This can be calculated by the following formula.

$$\text{Hausner Ratio (HR)} = \frac{\text{Tapped Density}}{\text{Bulk Density}}$$

Values less than 1.25 indicate good flow (=20% carr), and greater than 1.25 indicates poor flow (=33% carr). Between 1.25 and 1.5, added glidant normally improves flow (Trinadharao et al.,2015 and Devendra Revanand Rane *et al*., 2012).

f) Drug content

The Powder blend containing 10 mg equivalent of drug weighed and dissolved in methanol, then the volume is made upto 100ml with distilled water. From the above solution, 10 ml is taken and diluted with distilled water. The absorbance of resulting solution is measured at 234 nm using UV spectrophotometer (Shimadzu UV-1700 pharma spec, Japan) and the drug content is estimated.

8. POSTCOMPRESSIONAL EVALUATION OF LIQUISOLID TABLETS

a) General appearance

The formulated tablets are evaluated for general appearance such as colour, shape and appearance (Prasanth Sai R.V *et al*., 2011).

b) Thickness

Three tablets are randomly selected from each formulations and thickness is measured individually by vernier caliper. It is expressed in millimeter (mm) and average is calculated. (Amit modi *et al*., 2012).

b) Hardness

Hardness is defined as the "force required to break a tablet in the diametric compression test." Hardness is hence, also termed as the tablet crushing strength. The resistance of tablets to breakage under conditions of storage, transportation or handling

before usage depends on its hardness. Tablet hardness was measured with Pfizer tester. The tablet was held between a fixed and moving jaw. The scale was adjusted to zero and load was gradually increased until the tablet fractured. The value of the load at that point gives a measure of the hardness of the tablet. Hardness was expressed in kg/cm2. Hardness was reported in Table (Monali kalbhor et al.2017)

c) Weight variation

The test was performed as per USP by weighing 20 tablets individually on electric balance, calculating the averageweight, and comparing the individual tablet weight to the average weight.(srinivasarao et al.,2015)

Table 5 :Limits for weight variation test

AVERAGE WEIGHT	MAXIMUM % DIFFERENCE ALLOWED
130 mg or less	± 10%
130 mg to 324 mg	± 7.5%
More then 324 mg	± 5 %

d) Friability Test

This test is performed to evaluate the ability of tablets to withstand abrasion in packing, handling and transporting. Friability generally reflects poor cohesion of tablet ingredients. The initial weight of 10 tablets is taken and these are placed in the friability, which is consist of a circular plastic chamber, divided into 2-3 compartments. The chamber rotating at 25 rpm for 4min and drops the tablets by a distance of 15cm and

gives 100 revolutions. After that, the tablets are weighed once again. The difference in the weight is noted and expressed as the percentage. It should be preferably below 1.0%. Friability was reported in Table (Pooja et al.,2015 and Anand Kishore *et al*., 2011).

$$\% \text{ Friability} = \frac{W1 - W2}{W1} \times 100$$

Where,

W1= weight of tablets before test,

W2 = weight of tablets after test

e) Drug content

The total amount of drug present in the liquisolid formulation is evaluated using UV spectrophotometric analysis. Approximately weighed quantity of 10mg equivalent of drug is taken from liquisolid formulation which is dissolved in 10ml of methanol and the volume is made upto 100ml with distilled water. From the above solution, 10 ml is taken and diluted with distilled water. The absorbance of resulting solution (10µg/ml) is measured at 234 nm using spectrophotometer (shimadzu UV- 1700 pharma spec, Japan) and the drug content is calculated from the standard curve using the formula (Srinivas Vaskula *et al*., 2012).

$$\text{Drug content} = \frac{Samble\ absorbance}{Standard\ absorbance} \times 100$$

f) Disintegration test

Disintegration is defined as that state in which no residue of the tablet or capsule remains on the screen of the apparatus. The disintegration time of the liquisolid tablets is determined using disintegration test apparatus. Introduce one tablet into each tube and floating of the tablets can be prevented by placing a perforated plastic disc to each tube. Suspend the basket rack in the beaker containing the 900 ml of distilled water at 37 ^{o}C and move the basket containing the tablets up and down through a distance of 5-6 cm at a frequency of 28-32 cycles per minutes and the disintegration time for each formulations is noted (Indian Pharmacopoeia.,1996. Page no: A-80 to A-81).

Disintegration time

a) Uncoated tablets: 5- 30 minutes

b) Coated tablets: 1-2 hours

9. *IN VITRO* RELEASE STUDIES

In vitro release studies is performed by using USP type II Paddle dissolution apparatus in 900 ml of Phosphate buffer pH 7.4 maintained at 37° C **±** 0.5° C and rotation speed of 50 rpm. Samples (5 ml) are withdrawn at suitable time intervals (5, 10, 15,20, 25, 30, 45, 60 minutes) and filtered through whatman filter paper. Sink conditions are maintained throughout the study. The withdrawn samples are analyzed by UVvisible spectrophotometer (Shimadzu UV-1700 pharma spec, Japan) at λ max of 234nm. The studies are done in triplicate (Dinesh M. Pardhi *et al*., 2010 and www.fda.gov)

10. POWDER X-RAY DIFFRACTION STUDIES

Powder X-ray diffraction pattern of Pioglitazone hydrochloriude, Avicel PH102, Aerosil 200 and liquisolid formulation (Best formulation) are studied using X-ray diffractometer (XRD-462, Digaku, Japan) with CuKα radiation. Voltage and current are set 40 kV and 30 mA respectively. All pattern scanned over range 3-50^{o} 2θ angle with a scan speed of 2^{0}/min (Jahnavi N *et al*., 2013).

11. ASSESSMENT AND COMPARISON OF DRUG DISSOLUTION RATES

The dissolution rate of pioglitazone hydrochloride is the amount of drug (in μg) dissolved per minute by each tablet formulation during first 10 min is calculated by the following equation (Shashidher Burra *et al*., 2011 and Spireas et al., 1998)

$$D_R = \frac{(M \times D)}{1000}$$

Where,

M = Total amount of pure drug in each tablet (in μg)

D = Percentage of drug dissolved in the first 10 minutes

12. SELECTION AND EVALUATION OF BEST FORMULATION

The best formulation is selected depending on the results obtained from solubility studies in various non-volatile liquid vehicles and *in vitro* release studies

a) Comparison with directly compressed tablets

The *invitro* release of best formulation is compared with directly compressed tablets are prepared by mixing all tablet excipients, except non-volatile liquid vehicle (Amal Ali Elkordy *et al*., 2012 and Spiro Spireas et *al*., 1998)

b) Infrared spectroscopic studies for best formulation

Liquisolid formulation (Best formulation) is subjected to infrared Spectroscopic studies as per the procedure already discussed in compatibility studies.

c) Differential Scanning Colorimetric (DSC) studies for best formulation

DSC was performed using Shimadzu differential scanning calorimeter Mettler, in order to assess the thermotropic properties and thermal behaviour of the pure drug , and the liquisolid formulation (Best formulation). About 5 mg of the sample were sealed in the aluminium pans and heated at the rate of 10°C/min, covering a temperature range of 30°C to 300°C.(*Jabbar et al.2013)*

d) RELEASE KINETICS STUDIES

1. Zero – order model: Drug dissolution from dosage forms that do not disaggregate and release the drug slowly can be represented by the equation:

$$Qt = Q0 + K0t$$

Where,

Qt is the amount of drug dissolved in time t,

Q0 is the initial amount of drug in the solution,

K0 is the zero order release constant and

“t” is time in hours.

Expressed in units of concentration/time.

Graph: X- axis is time in hours and Y- axis is % cumulative drug release.

2. First order model: The release of the drug which followed first order kinetics can be expressed by the equation:

observed in final formulation, which indicates that the pioglitazone was molecularly dispersed and in an amorphous form (Sanjeev Gubbi *et al*., 2009 and Abdul Hasan Sathali A. and Deepa C. *et al*., 2013)

$$\log Qt = \log Q0 + Kt / 2.303$$

Where,

Q0 is the initial concentration of drug,

Qt is cumulative amount of drug released per unit surface area,

k is the first order rate constant and “t” is the time.

Graph: X- axis is time in hours and Y- axis is log % cumulative drug release.

3. Hixon Crowell model: Hixson and Crowell (1931) recognized that the particles regular area is proportional to the cube root of its volume. The equation describes the release from systems where there is a change in surface area and diameter of particles. They derived the equation:

$$W01/3 - W1/3 = KHC * t$$

Where,

W0 is the initial weight of particle,

W is the weight of particle, KHC is Hixon Crowell release rate constant and “t” is time.

4. Higuchi model:

Higuchi model describes the drug release from several type of matrices initially conceived for planar systems, then extended to different geometrics and porous systems. It was derived by higuchi in 1961. For higuchi release kinetics equation

Q = KH t 0.

Where,

Q is amount of drug released per unit surface area of the dosage form

KH is Higuchi release rate constant and

"t" is time.

5. Korsmeyer – Peppas model: Koresmeyer derived a simple relationship which describes drug release from a polymeric system. To find out the mechanism of drug release, first 60% drug release data was fitted in Koresmeyer – Peppas model equation,

(Mt/M) = Km tn

where,

Mt is amount of drug released at time t,M is total amount of drug in dosage form,Km is kinetic constant,n is diffusion and release exponent and t is time in hours

d)Stability studies

The best formulation of three batches is stored at 40° C ± 2°C and relative RH 75% ± 5% for two months. The best formulation is evaluated using dissolution test, drug content, physical appearance, hardness and thickness. The above tests of best formulations are compared with those of freshly prepared tablets.

(Prasanth Sai R.V *et al*., 2011 and Amit Modi *et al*., 2012).

CHAPTER-9

RESULTS AND DISCUSSION

CHAPTER-IX

RESULTS AND DISCUSSION

1.PREPARATION OF STANDARD CALIBRATION CURVE

The λmax of Pioglitazone hydrochloride was determined by scanning the (10µg/ml) solution of drug in phosphate buffer Ph 7.4 by UV-spectrophotometer and it was found to be 234nm((Pragati Shakya* and Kuldeep Singh., 2010) **(Figure 5)**. The absorbance of the solution (5-25 µg/ml) was measured in UV-spectrophotometer at 234 nm. The linear correlation coefficient was found to be γ = 0.9998. The results were shown in **Table 6**and the calibration graph of Pioglitazone hydrochloride was shown in **Figure 6.**

2. SOLUBILITY STUDIES

The solubility of pioglitazone hydrochloride was determined in various non-volatile liquid vehicles such as Propylene glycol (PG), Polyethylene glycol (PEG 400), Tween 80, Capryol 90 and in distilled water shown in **Table 7** and **Figure 7**. From the results, it was observed that the solubility of drug in Tween 80 was higher when compared with other liquid vehicles which may be due to the high viscosity and HLB value Prasanna et al., 2015)

3. PREFORMULATION (COMPATIBILITY) STUDIES

a) Infrared Spectroscopic Studies

Infrared (IR) spectroscopic studies were carried out to confirm the compatibility between drug and excipients used for the preparation of liquisolid tablets. The IR

studies were performed for pioglitazone hydrochloride (pure drug), non-volatile liquid vehicle, microcrystalline cellulose, aerosil 200 and physical mixture of drug and excipients. The spectra studied at 4000cm-1 to 400 cm-1 were shown in **Figure 8**

The principal peaks for pure drug were observed at wave numbers 3415.93 cm^{-1}, 3363.96 cm^{-1}, 1639.49 cm^{-1}, 1608.63 cm^{-1}, 1294.24 cm^{-1}, 1176.58 cm^{-1}, Further in the physical mixtures, all the above characteristics peaks of the drug appear in the spectrum, which indicated that there was no interaction between the drug and polymers in the physical mixture

Further in the physical mixtures, all the above characteristics peaks of the pure drug appear in the spectrum, which indicated that there was no interaction between the drug and polymers in the physical mixture.

4. FLOWABLE LIQUID-RETENTION POTENTIAL (Φ-VALUE) FOR EXCIPIENTS

Angle of slide was used to determine the Φ-value for the excipients (which are needed for calculation of the Lf). The ΦCA-value (carrier) and ΦCO-value (coating material) decided the appropriate quantities of carrier and coating materials required to convert a given amount of liquid medication into a dry-looking, free flowing and readily compressible liquisolid formulation. Flowable liquid-retention potential values for excipients were taken from literature (Spireas *et al*., 1998)

The flowable liquid- retention potential (Φ-value) for Avicel PH 102 carrier in

- ✓ Propylene glycol was approximately 0.16
- ✓ Polyethylene glycol was approximately 0.005

- ✓ Tween 80 was approximately 0.003

The flowable liquid- retention potential (Φ-value) for Aerosil 200 coating material in

- ✓ Propylene glycol was approximately 3.31
- ✓ Polyethylene glycol was approximately 3.26
- ✓ Tween 80 was approximately 3.95

The relatively high Φ -value is advantageous as it results in smaller sizes of the tablets. The above values were used to formulate liquisolid tablets of Pioglitazone hydrochloride (Amal Ali Elkordy *et al*., 2013).

5. PROCEDURE FOR PREPARATION OF LIQUISOLID POWDER

Liquisolid powder of pioglitazone hydrochloride were prepared using different non-volatile liquid vehicle(Propylene glycol,Polyethylene glycol 400,Tween 80) at ratio of (1:1) drug: liquid vehicles. The microcrystalline cellulose (Avicel PH102) was used as a carrier and silica (Aerosil 200) as coating material. Finally 5% (w/w) crospovidone as a super disintegrant and 0.75% (w/w) of magnesium stearate as a lubricant were added and mixed. All liquisolid preparations were compacted into tablets using a multi punch tablet machine (Fluid pack, Ahmedabad) having 10mm flat punch. The compositions of all the formulations were given in **Table**.**8** Twelve formulations (F1- F12) were prepared.(Prasanna MV et al.,2015)

6. PREPARATION OF DIRECTLY COMPRESSED TABLETS

A conventional formulation of pioglitazone hydrochloride were prepared by using drug (Pioglitazone hydrochloride),Microcrystalline cellulose (Avicel PH 102), Silica (Aerosil

200) and sodium starch glycolate, without addition of any non-volatile liquid vehicles. The composition of the formulation was given in **Table 9**

7. PRECOMPRESSIONAL EVALUATION OF POWDER BLEND

Powder flow is a critical character that might affect uniformity of the tablet weight. Therefore, the flow properties of the powder blend of all liquisolid formulations were determined in order to calculate that the amount of carrier and coating materials were required to maintain acceptable flow and compaction properties. The powder blend of all formulations was evaluated for precompression parameters such as angle of repose, bulk density, true density, carr's index, Hausner's ratio and drug content

a) Angle of Repose

The angle of repose is a characteristic of the internal friction or cohesion of the particles, the value will be low, if the powder is non-cohesive and high if the powder is cohesive. All the prepared formulations were in the ranges from $26^{'}.24^{O}$ to 33.39^{O}, which indicates the good flow properties of liquisolid powder. The results of angle of repose of all formulations were shown in **Table 10 and Figure 10**

b) Bulk density

Bulk density was used to measure the flow properties of the powder. The bulk density of the powder blend was in the range of 0.206 gm/ml to 0.855 gm/ml. The results of bulk density for all the formulations were shown in **Table 10 and Figure 11**

b) Tapped density

The tapped density of the powder blend was in the range of 0.250 gm/ml to gm/ml. The results of bulk density for all the formulations were shown in **Table 10 and Figure 12**

c) Carr's Index (CI)

Determination of carr's index, the ratio of bulk and tapped density, was used to measure the flow property of all liquisolid formulations. The decrease the value of the CI% would indicate the better flow properties of the powder. The carr's index of the all formulations was found to be in range of 9.55% to 14.56%. It was less than 25%, which indicates that the powder blend have required flow property for compression of tablets. The results of carr's index of all formulations were shown in **Table 10 and Figure 13**

b) Hausner's Ratio

The Hausner's ratio of all the formulations was found to be in range of 1.01 to 1.19, which indicates better flow property of the powder blend. The results were shown in **Table 10 and Figure 14**

c) Drug content

The percentage drug content for all formulations was found to be in the range of 96.12% to 99.88%, ensured the uniformity of the drug content. The results indicated all the formulations were within the limits as per IP (Limit: not less than 85% and not more than 115%). The results were shown in **Table 13** and **Figure 15**.

All the above precompressional evaluations were done for directly compressed tablets and they were within the limit (**Table 11**).

8. POSTCOMPRESSIONAL EVALUATION OF LIQUISOLID TABLETS

Tablets of different formulations were evaluated for the postcompressional parameters such as general appearance, weight variation, hardness, thickness, friability, disintegration time and drug content for tablets.

a) General appearance

The formulated tablets were white in colour, biconvex and round shape. All the tablets were elegant in appearance. The results were shown in the **Table 12.**

b) Thickness

The thickness of all the tablet formulations was used to determine the uniformity of size and shape of the tablets. All the prepared tablet formulations were measured by vernier caliper and were found to be in the range of 2.45 to 5.2mm. The results indicated that all the formulations had uniform size and shape. The results were shown in **Table 12.**

c) Hardness

Hardness of tablet was used to determine the resistance to withstand mechanical shakes of handling in manufacture and packing. All the prepared tablets were determined using Monsanto hardness tester. The hardness of all the formulations was found to be 4 to 5 Kg/cm2, which indicates that all the tablet formulations had good mechanical strength. The results of all the formulations were shown in **Table 12.**

d) Weight variation

The weight was used to ensure the uniformity of the tablet in all formulations. All the formulation tablets passes the weight variations within the acceptable limits as per IP.the results were shown in **Table 12.**

e) Friability test

The friability of tablets was determined using Roche friabilator and used to determine the mechanical strength of tablets.the percentage friability of all the tablet formulation was found to be in the range of 0.20 to 0.64 %. It was less then 1% the results indicated that all the tablets formulation had a good mechanical resistance of tablets. The results were shown in **Table 12**

f) Drug content

The drug content was used to determine the uniform amount of active ingredients presenty in all the formulations. The drug content was found to be in the range of 96.12% to 99.88% which indicates all the formulations were within the acceptable limits as per IP (Limits not less then 85% and not more then 115%) The results were shown in **Table 11**

d) Disintegration test

The disintegration time of all the tablet formulations was determined using disintegration test apparatus. All the prepared tablet formulations were in between 3 min 30 sec to 8 min 7 sec. it was lesser then 15 minutes. Which indicates all the

All the above postcompressional evaluations were done for directly compressed tablets and they were within the limit.**(Table 12)**

9. *INVITRO* RELEASE STUDIES

In vitro dissolution studies were carried out by USP type II method by using Phosphate buffer pH 7.4 as a medium. The samples were taken at an interval of 10min absorbance was measured in UV spectrophotometer at 234nm.

Two formulation parameters such as effect of drug concentration in the liquid medication (ratio of drug and liquid vehicle) and effect of carrier/coating ratio (R value) that would affect the drug dissolution rate in immediate release liquisolid tablets were investigated.

The results of *in vitro* release studies from liquisolid formulations shown in

(Table 15a,15b and Figure 16a to 16d)

Formulations F1, F2, F3, and F4 were prepared with 1:1,(ratio of drug and Propylene glycol) 5:1, 10:1, 15:1 and 20:1 (ratio of MCC & Aerosil 200) showed the cumulative % of drug release 95.67%,93.79%,92.01%, and 94.10% .

Formulations F5, F6, F7, and F8 were prepared with 1:1,(ratio of drug and Polyethylene glycol-400) 5:1, 10:1, 15:1 and 20:1 (ratio of MCC & Aerosil 200) showed the cumulative % of drug release 94.00%,93.27%,95.81% and 96.23%

Formulations F9, F10, F11, and F12 were prepared with 1:1,(ratio of drug and Tween 80) 5:1, 10:1, 15:1 and 20:1 (ratio of MCC & Aerosil 200) showed the cumulative % of drug release 95.36%,94.94% 97.07% and 98.74%. The formulation which showed highest release among all the formulations was F12 (98.74%)

F12>F11>F8>F7>F1>F9>F10>F4>F5>F2>F6>F3

From the above results, it was observed that the drug release was faster for formulation F12, containing the ratio 1:1 (drug:Tween 80). The enhanced drug dissolution rate may be mainly attributed to the fact that this poorly water-soluble drug is already in solution in Tween 80, while at the same time, it is carried by the powder particles (microcrystalline cellulose-silica) of liquid vehicle. Thus, its release is

accelerate due to its markedly increased wettability and surface availability to the dissolution medium.

Microcrystalline cellulose and Aerosil 200 were used as carrier and coating materials, respectively in prepared formulations. The effect of carrier and coating material ratio (R-value) on the drug dissolution were investigated. Two R-value of 5,10,15 and 20 were studied. Generally, the higher R-value showed higher drug dissolution than the lower R-value.

It was observed that formulation F12 with higher R-value showed a higher drug release than the formulation with lower R-value. Liquisolid tablets with high Rvalue would contain high amount of microcrystalline cellulose (act as disintegrant), low amount of Aerosil 200 (hydrophobic in nature that would retard drug release) and low liquid load factor.

The overall results indicated that the prepared immediate release liquisolid tablet formulation (F12) at the ratio of 1:1 (drug: Tween 80) and the higher R-value (30) which improved the dissolution behavior of drug (Nokhodchi. A *et al*., 2005).

Among all the 12 formulations, F12 was selected as a best formulation which had the better drug release rate (98.74% at 1hour). Accordingly, this improved drug release may result in a higher drug absorption in the gastrointestinal tract and thus, an improved oral bioavailability.

10. POWDER X-RAY DIFFRACTION STUDIES

Polymorphic changes in the drug are important factor which might affect the dissolution rate of drug and in turn bioavailability. So that it is necessary to study the

polymorphic changes of pure drug in liquisolid systems. The crystalline nature of drug was studied by the characteristic PXRD pattern which showed sharp peaks at 18^{o},20^{o},28^{o},and 30^{o} positions. PXRD for pure drug, excipients and liquisolid systems were showed in **Figure 10a & 10b**

Liquisolid powder x ray diffraction pattern showed absence of these characteristic peaks of drug, which indicated pure drug, was entirely converted into amorphous or solubilized from. Theabsence of crystalinity in the liquisolid formulation might be due to solubilization ofdrug in liquid vehicle that is possibly absorbed and adsorbed on the carrier and coating material. The amorphization or solubilization of pure drug may result in an enhancement of dissolution rate (Sanjeev Ragavendra Gubbi *et al*., 2010 and Abdul Hasan Sathali A. and Deepa C. *et al*., 2013).

11. ASSESSMENT AND COMPARISON OF DRUG DISSOLUTION RATES

The concentration of drug and Tween 80 is one of the main factors for the formulation of a liquisolid tablets and has considerable effect on the 10 min dissolution rate. Dissolution rate increased with an increase in the concentration of Tween 80 due to high molecular dispersion states of the drug in the formulations. The results were shown in **Table 17.** The comparison of dissolution rate for pure drug, directly compressed tablets and liquisolid formulation were shown in **Table 18** and

Figure 12

Formulations F1, F2, F3, and F4 were prepared with 1:1, (ratio of drug and Propylene glycol) and R-value of 5,10,15 and 20 showed the dissolution rate of 100.60 µg/min, 97.70 µg/min, 120.48 µg/min, and 124..82 µg/min, respectively at 10 min.

Formulations F5, F6, F7, and F8 were prepared with 1:1, (ratio of drug and Polyethylene glycol-400) and R-value of 5,10,15 and 20 showed the dissolution rate of 127.27 µg/min, 135.24 µg/min, 120.48 µg/min, and 136.34 µg/min, respectively at 10 min.

Formulations F9, F10, F11, and F12 were prepared with 1:1, (ratio of drug and Tween 80) and R-value of 5,10,15 and 20 showed the dissolution rate of 114.41 µg/min, 127.91 µg/min, 153.00 µg/min, and 182.27 µg/min, respectively at 10 min. Among the Twelve formulations F12 showed maximum dissolution rate of 182.27 µg/min.

The dissolution rate of pure drug, directly compressed tablet and liquisolid formulation were showed 41.30 µg/min, 95.66µg/min and 182.27 µg/min respectively. As it clear from the figure 12, the liquisolid tablets displayed higher dissolution rate than those of directly compressed tablet and pure drug.

According to the classic dissolution equation:

$$DR = (D/h)\ S\ (CS - C)$$

The drug dissolution rate (D_R) of a drug is directly proportional to its concentration gradient (C_s–C) in the stagnant diffusion layer and its surface (S) available for dissolution. C_s is the saturation solubility of the drug in the dissolution medium and, thus, it is a constant characteristic property related to the drug and dissolving liquid involved. Since all of dissolution tests for formulations were done at a constant rotational paddle speed (50 rpm) and identical dissolving media, we can assume that the thickness (h) of the stagnant diffusion layer and the diffusion coefficient (D) of the drug molecules remain almost identical. Therefore, the observed higher

dissolution rates of paliperidone from liquisolid tablets are due to the significantly increased surface of the molecularly dispersed pioglitazone. In addition, the saturation solubility of the drug in the microenvironment (*C*s) might be increased in the liquisolid systems due to the presence of Tween 80. So, such an increase in *C*s, in a larger drug concentration gradient, increases the dissolution rate of pioglitazone according to the Noyes Whitney equation (Dinesh M. Pardhi et al., 2010 & Nokhodchi A. *et al*., 2005).

12. SELECTION AND EVALUATION OF BEST FORMULATION

From the above results of characterization F20 was selected as the best formulation.

1. Solubility of drug in Tween 80 – 14.124 (mg/10ml)

2. In vitro release studies - 98.74% at 60 min

1. Comparison of dissolution studies of best formulation with pure drug and directly compressed tablets

The *in vitro* dissolution studies of best formulation (F12) were compared with pure drug and directly compressed tablets. The cumulative percentage of drug in formulation was found to be 98.74% in 1 hour compared to the pure drug and directly compressed tablets whose cumulative percentage drug release was found to be 22.00% & 42.59% in 1 hour, respectively. Thus the formulation F12 showed higher drug release than the pure drug and directly compressed tablets. The results were shown in **Table 19** and **Figure 13**.

2. Infrared spectroscopic studies

Infrared spectrum was performed for the liquisolid formulation, the major peaks of the drug still shown in the spectrum at 3510.45 cm-1, 3396.64 cm-1 , 2922.16 cm-1,2358.98 cm-1,1647.21 cm-1, 1560.77 cm-1, 1249.02 cm-1, 1114.86 cm-1, 1016.49cm-1, 857.73 cm-1 indicated that there was no interaction between the drug and polymers in the preparation of liquisolid compacts. The result was shown in **Figure**

3. Differential scanning colorimetric studies

The DSC thermogram of pure drug, excipients and final formulation were shown in **Figure 9a to 9b.** Pure pioglitazone showed a sharp endothermic peak at 193.88°C corresponding to its melting temperature 192.13. Such sharp endothermic peak signifies that pioglitazone used was in pure crystalline state. Microcrystalline cellulose showed sharp endothermic peak at 100.50 °C. The thermal behavior of aerosil 200 did not show any sharp endothermic peak and hence, the aerosil 200 was in an almost amorphous state. The sharp endothermic peak of pure drug was not

4. DRUG RELEASE KINETIC MODEL

In order to describe the kinetics of the release process of drug in all formulations, equations such as zero-order and first- order rate equations were used. Zero order rate equation describes the system where the release rate is independent of the concentrations of the dissolved species. While the first- order equation describes the release from systems where dissolution rate is dependent on the concentration of the dissolving species. It is evident from **Table 19, and 19B** that the drug release process is not zero order in nature. This indicates that the dissolution rate of the drug is not

independent of the amount of drug available for dissolution and diffusion from the matrix. The dissolution data of all formulations when fitted in accordance with the first order equation it is evident that a linear relationship was obtained with 'r' (correlation coefficient) value close to unity and higher than 'r' obtained from zero order equation for all formulation (table), showing that the release is an apparent first order process. This indicates that the amount of drug released is dependent on the matrix.

The obtained from *invitro* dissolution studies were fitted to zero –order, first-order and Korsmeyer Peppas equation. The first-order plots were found to be fairly linear as indicated by their high regression values. To confirm the exact mechanism of drug release, the data were fitted according to Korsmeyer Peppas equation:

$$Mt/m\infty = k\ t^{n}$$

where mt/m∞ is fraction of drug released, k is kinetic constant, t is release time and *n* is the diffusional exponent for drug release. Peppas stated that the above equation could adequately describe the release of solutes from slabs, spheres, cylinders and discs, regardless of the release mechanism. The value of '*n*' gives an indication of the release mechanism; when *n* =1, the release rate is independent of time (zero-order) (case II transport), *n* = 0.5 for Fickian diffusion and when 0.5 < *n* <1.0, diffusion and non-Fickian transport are implicated. Lastly,when *n* > 1.0 super case II transport is apparent. '*n*' is the slope value of log mt/m∞ versus log time curve**.** Slope values (*n* > 1.0) suggest that the release of cilnidipine from orodispersible tablets followed Supercase-II transport suggesting that more than one mechanism may be involved in the release kinetics. The results were shown in **Figure 19a and 19b.**

14.Stability studies

The stability studies were investigated whether the physical chemical parameters and dissolution of liquisolid tablets is affected by storage under a 40° C ± 2°C and 75%± 5% RH. The best formulation of three batches is stored at 40° C ± 2°C and 75%± 5% RH for two months. The results showed no significant changes in physical appearance, hardness, thickness, drug content and dissolution test of aged tablets compared to the fresh liquisolid tablets. This indicates that the liquisolid tablets were stable under these storage conditions. The results were shown in **Table 20 and Figure 25.**

TABLE 6: CALIBRATION OF PIOGLITAZONE HYDROCHLORIDE IN PHOSPHATE BUFFER pH 7.4

S.NO	CONCENTRATION (µg/ml)	ABSORBANCE ± SD*
1.	5	0.173 ± 0.03
2.	10	0.307 ± 0.06
3.	15	0.443 ±0.08
4.	20	0.588 ± 0.12
5.	25	0.729 ± 0.13

n=3* γ = **0.9998**

TABLE 7 : DETERMINATION OF SOLUBILITY OF PIOGLITAZONE HYDROCHLORIDE DIFFERENT NON-VOLATILE LIQUID VEHICLES

S.NO	NON-VOLATILE LIQUID VEHICLES	SOLUBILITY (mg/10ml) ±SD*
1.	PROPYLENE GLYCOL	9.201 ± 0.15
2.	PEG-400	8.331 ± 0.14
3.	TWEEN 80	14.124 ± 0.16
4.	CAPRYOL 90	8.657 ± 0.09
5.	DISTILLED WATER	1.204 ± 0.07

n=3*

PEG 400 = Polyethylene Glycol 400, Tween 80 = Polysorbate,

CAPRYOL 90 = Propylene Glycol Monocaprylate

TABLE 8 : COMPOSITION OF PIOGLITAZONE HYDROCHLORIDE LIQUISOLID TABLET

Formulation Code	Non- volatile liquid vehicle	R	Active Ingredient (mg)	Liquid Vehicle (mg)	Lf	Avicel PH102 Q (mg	Aerosil 200 q (mg)	Disintegrant [Crospovidone] (mg)	Magnesium Stearate (mg)	Talc (mg)	Total Weight Of tablet (mg)
F1	Propylene glycol	5	30	30	0.822	36.49	3.6	5.3	0.793	1.06	107.24
F2	Propylene glycol	10	30	30	0.491	61.09	6.1	6.75	1.0	1.0	135.94
F3	Propylene glycol	15	30	30	0.380	78.94	7.8	7.75	1.15	1.54	157.18
F4	Propylene glycol	20	30	30	0.325	92.30	9.2	8.07	1.2	1.69	172.59
F5	Polyethylene glycol- 400	5	30	30	0.657	45.66	4.5	5.50	0.86	1.16	117.68
F6	Polyethylene glycol- 400	10	30	30	0.331	90.63	9.6	7.98	1.25	1.68	170.54
F7	Polyethylene glycol- 400	15	30	30	0.222	135.13	13.51	10.43	1.64	2.2	222.91
F8	Polyethylene glycol- 400	20	30	30	0.168	178.57	17.85	12.82	2.0	2.7	273.94
F9	Tween80	5	30	30	0.793	37.83	3.7	5.07	0.79	1.0	108.39
F10	Tween80	10	30	30	0.398	75.37	7.5	7.14	1.12	1.5	152.63
F11	Tween80	15	30	30	0.266	112.78	11.2	9.19	1.44	1.9	196.51
F12	Tween80	20	30	30	0.200	150	15	11.25	1.77	2.3	240.32

Tween 80 = Polysorbate 80, R= Carrier and coating material ratio, L_f = Liquid load factor, $Q=W/L_f$(Q=Carrier material and W= Total weight of drug and liquid vehicle), q=Q/R (q=Coating material).

Table 9: COMPOSITION OF DIRECTLY COMPRESSED TABLETS

S.No	Ingredients	Quantity for one tablet (mg)
1	Pioglitazone hydrochloride	30
2	Avicel PH102	184.12
3	Aerosil 200	17.85
4	Crospovidone	12.82
5	Magnesium stearate	2.0
6	Talc	2.7

Total weight = 249.49mg

TABLE 10: PRECOMPRESSIONAL EVALUATION OF POWER BLEND

Formulation code	Angle of repose θ ± SD*	Bulk density (g/ml) ± SD*	Tapped density (g/ml) ± SD*	Carr 's Index (%)± SD*	Hausner 's ratio ± SD*
F1	33.37±1.54	0.802 ±0.05	0.877 ± 0.01	12.16 ± 0.84	1.096 ± 0.05
F2	32.98±1.83	0.806 ±0.02	0.896 ± 0.02	12.00 ± 1.55	1.112 ± 0.05
F3	32.96±1.73	0.820 ±0.01	0.935 ± 0.02	11.94 ± 1.77	1.146 ± 0.04
F4	34.16±1.83	0.832 ±0.01	0.937 ± 0.02	12.34 ± 0.81	1.074 ± 0.01
F5	31.69±0.67	0.841 ±0.01	0.926 ± 0.02	12.3 ± 0.72	1.099 ± 0.03
F6	33.15±1.12	0.834 ±0.00	0.912 ± 0.00	9.26 ± 0.94	1.017 ± 0.02
F7	31.66±1.58	0.816 ±0.01	0.940 ± 0.02	9.55 ± 0.65	1.146 ± 0.03
F8	32.79±0.47	0.813 ±0.01	0.935 ± 0.02	13.17 ± 1.02	1.192 ± 0.04
F9	29.55±0.76	0.817 ±0.00	0.921 ± 0.01	9.96 ± 0.92	1.055 ± 0.02
F10	31.27±1.63	0.806 ±0.01	0.939 ± 0.02	13.8 ± 0.52	1.159 ± 0.03
F11	28.81±0.52	0.832 ±0.01	0.925 ± 0.00	12.23 ± 0.93	1.121 ± 0.02
F12	26.24±0.42	0.852 ±0.01	0.939 ± 0.01	13.53 ± 0.40	1.140 ± 0.00

n=3*

TABLE 11 : DRUG CONTENT OF PIOGLITAZONE HYDROCHLORIDE POWDER BLEND

S.No	Formulation Code	Drug content (%) ± SD*
1	F1	96.12 ± 0.00
2	F2	97.86 ± 0.57
3	F3	96.30 ± 0.42
4	F4	97.15 ± 0.98
5	F5	98.53 ± 0.52
6	F6	96.20 ± 0.81
7	F7	98.36 ± 0.56
8	F8	97.48 ± 0.56
9	F9	97.30 ± 0.66
10	F10	98.11 ± 0.18
11	F11	98.59 ± 0.18
12	F12	99.88 ± 0.37

n=3*

TABLE 12: POST COMPRESSIONAL EVALUATION OF LIQUISOLID TABLETS

Formulation Code	General appearane	Hardness (kg/cm^2)	Thickness (mm)	Weight variation (mg)	Friability (%)	Disintegration time (sec)
F1	White colour	4	2.54	107.45-110.12	0.64	6 min 12 sec
F2	White colour	4	3.20	136.67-139.85	0.52	6 min 32 sec
F3	White colour	5	3.38	157.56 – 160	0.24	6 min 40 sec
F4	White colour	4	2.68	173.12 176.21	0.41	5 min 32 sec
F5	White colour	5	2.42	117.28 -120.12	0.52	6 min 51 sec
F6	White colour	4	3.21	171 -174.32	0.36	5 min 36 sec
F7	White colour	4	3.92	223.45-225.1	0.24	5 min 12 sec
F8	White colour	5	4.17	274.12-277.21	0.29	5min 35 sec
F9	White colour	4	3.85	109-112.12	0.64	4 min 57 sec
F10	White colour	4	4.47	153.12- 156.21	0.47	4 min 48 sec
F11	White colour	4	4.75	197.21 -199.21	0.30	4 min 12 sec
F12	White colour	5	4.81	241.21-243.47	0.20	3 min 48 sec

n=3*

TABLE 13: DRUG CONTENT OF PIOGLITAZONE HYDROCHLORIDE LIQUISOLID TABLET

S.No	Formulation code	Drug content (%) ± SD*
1	F1	99.12 ± 0.31
2	F2	99.29 ± 0.25
3	F3	99.25 ± 0.27
4	F4	99.56 ± 0.45
5	F5	99.45 ± 0.32
6	F6	99.87 ± 0.54
7	F7	99.28 ± 0.28
8	F8	99.34 ± 0.24
9	F9	99.24 ± 0.21
10	F10	99.29 ± 0.54
11	F11	99.84 ± 0.18
12	F12	99.78 ± 0.36

n=3*

TABLE 14a : PRECOMPRESSIONAL EVALUATION FOR DIRECTLY COMPRESSED TABLETS

S.No	PARAMETERS	VALUES
1	Angle of repose ± SD	24.26 ± 0.22
2	Bulk density ± SD	0.678 ± 0.01
3	Tapped density ± SD	0.725 ± 0.04
4	Carr's index ± SD	8.78 ± 0.34
5	Hausner's ratio ± SD	1.10 ± 0.01
6	Drug content ± SD	98.78 % ± 0.32

TABLE 14b : POST COMPRESSIONAL EVALUATION FOR DIRECTLY COMPRESSED TABLETS

S.No	PARAMETERS	VALUES
1	Hardness	4 kg/cm^2
2	Thickness	3.25mm
3	Diameter	8mm
4	Weight variation	244.54 -249.49
5	Friability	0.24%
6	Drug content ± SD	98.95% ± 0.30
7	Disintegration time	7 min 45 sec

TABLE 15a: *IN VITRO* RELEASE PROFILE OF PIOGLITAZONE HYDROCHLORIDE LIQUISOLID FORMULATION

TIME IN MINUTES	CUMULATIVE PERCENTAGE DRUG RELEASE ± SD					
	F1	F2	F3	F4	F5	F6
10	10.60±1.26	9.77±2.05	12.48±1.91	12.48±1.88	12.27±1.73	13.52±1.65
20	21.79±2.70	23.99±1.48	23.26±1.13	24.20±1.13	22.52±1.88	29.00±4.65
30	37.26±2.85	49.27±2.19	53.35±1.88	48.86±2.51	49.90±2.36	56.90±4.23
40	53.35±3.18	67.98±1.10	58.57±0.78	77.91±4.82	73.93±2.13	71.95±5.21
50	78.22±3.12	83.23±2.55	72.99±4.03	85.32±2.36	83.44±3.61	84.38±2.87
60	95.67±1.13	93.79±1.56	92.01±5.42	93.16±0.94	94.00±2.20	93.27±2.55

n=3*

TABLE 15b: *IN VITRO* RELEASE PROFILE OF PIOGLITAZONE HYDROCHLORIDE LIQUISOLID FORMULATION

TIME IN MINUTES	CUMULATIVE PERCENTAGE DRUG RELEASE ± SD					
	F7	F8	F9	F10	F11	F12
10	12.48±1.78	13.63±0.65	11.44±2.51	12.79±0.72	15.30±1.00	18.22±1.22
20	29.82±2.81	30.76±2.19	28.69±2.91	30.15±0.18	34.73±1.57	42.35±3.44
30	53.73±1.78	54.46±1.91	48.02±4.92	51.78±1.99	56.34±3.77	68.46±2.66
40	79.42±2.91	84.12±2.01	76.76±4.40	77.28±1.98	78.06±3.13	87.36±2.22
50	86.21±1.25	87.46±1.43	87.10±0.78	86.68±1.26	92.16±1.56	95.08±0.78
60	95.81±1.91	96.23±2.44	95.36±1.95	94.94±1.28	97.07±1.18	98.74±0.62

n=3*

TABLE 16 : DISSOLUTION RATE OF DRUG AFTER 10 MINUTES

S.No	FORMULATION CODE	DISSOLUTION RATE AFTER 10 MINUTES (µg/ml)
1	F1	100.60
2	F2	97.70
3	F3	120.48
4	F4	124.82
5	F5	127.27
6	F6	135.24
7	F7	120.48
8	F8	136.34
9	F9	114.41
10	F10	127.91
11	F11	153.00
12	F12	182.27

TABLE 17 : COMPARISON OF DISSOLUTION RATE OF PURE DRUG, CONVENTIONAL TABLET AND BEST FORMULATION AFTER 10 MINUTES

DISSOLUTION RATE AFTER 10MINUTES(μg/ml)	
PURE DRUG	41.32
CONVENTIONAL TABLET	95.62
BEST FORMULATION	182.27

TABLE 18 : COMPARISON OF *IN VITRO* RELEASE PROFILE FOR PURE DRUG, CONVENTIONAL TABLET AND LIQUISOLID TABLET

CUMULATIVE PERCENTAGE DRUG RELEASE ±SD*						
TIME IN MINUTES	10	20	30	40	50	60
PURE DRUG	4.13±0.62	8.63±1.0	11.66±2.05	15.42±4.21	19.39±1.787	22.00±0.82
CONVENTIONAL TABLET	9.56±1.57	13.33±1.26	17.40±1.41	27.02±1.74	36.84±4.09	42.59±3.60
LIQUISOLID TABLET	18.22±1.12	42.35±3.44	68.46±2.66	87.36±2.22	95.08±0.78	98.74±0.62

TABLE: 19A *IN-VITRO* KINETIC RELEASE STUDIES LIQUISOLID TECHNIQUE FOR FORMULATION

FORMULATION CODE	ZERO ORDER		FIRST ORDER		HIGHUCHI MODEL		KORE'S MEYER MODEL		HIXON CROWELL	
	r^2	$K^0(h^{-1})$	r^2	$K_1(h^{-1})$	r^2	$K_H(h^{-1/2})$	r^2	n	r^2	$K_{HC}(h^{-1/3})$
F1	0.986	1.744	0. 7902	-0.0216	0.806	11.64	0.9944	1.2453	0.0016	0.0031
F2	0.935	1.761	0.9454	-0.0232	0.813	13.068	0.9879	1.3090	0.0009	0.0021
F3	0.973	1.577	0.8509	-0.0233	0.877	12.42	0.9746	1.361	0.0136	0.0083
F4	0.955	1.759	0.9627	-0.0246	0.995	19.54	0.9765	1.2068	0.0002	0.001
F5	0.968	1.758	0.9559	-0.0233	0.873	13.14	0.9748	1.2191	0.9802	-0.0543
F6	0.969	1.656	0.942	-0.023	0.904	13.006	0.9858	1.1626	0.9925	-0.0516

TABLE: 19B *IN-VITRO* KINETIC RELEASE STUDIES LIQUISOLID TECHNIQUE FOR FORMULATION

FORMULATION CODE	ZERO ORDER		FIRST ORDER		HIGHUCHI MODEL		KORE'S MEYER MODEL		HIXON CROWELL	
	r^2	$K^0(h^{-1})$	r^2	$K_1(h^{-1})$	r^2	$K_H(h^{-1/2})$	r^2	n	r^2	$K_{HC}(h^{-1/3})$
F7	0.971	1.7816	0.9602	-0.0248	0.892	13.393	0.987	1.2453	0.9813	-0.0578
F8	0.9682	1.758	0.9513	-0.0269	0.911	13.326	0.9858	1.3092	0.9914	-0.0546
F9	0.968	1.758	0.9412	-0.0267	0.895	13.587	0.987	1.1361	0.9839	0.0576
F10	0.9697	1.659	0.9178	-0.0295	0.898	13.479	0.977	1.2068	0.9732	-0.0592
F11	0.9698	1.722	0.9374	-0.028	0.918	13.801	0.987	1.2191	0.9861	-0.0618
F12	0.925	1.6542	0.9737	-0.0367	0.941	14.341	0.965	1.1626	0.9959	-0.0675

TABLE 20: DISSOLUTION PROFILE OF BEST FORMULATION (F12) AT 40^{O}C ± 2^{O}C AND 75% ± 5%

TIME IN MINUTES	CONTROL	25^{0}C (Room Temperature)		40^{0}C / 75% RH	
		15th day	30th day	15th day	30th day
10	18.44±1.04	18.30±0.91	18.60±1.07	18.13±0.69	18.27±0.88
20	42.35±1.01	41.81±0.75	42.20±1.01	41.33±0.58	42.17±0.97
30	68.73±1.10	68.04±0.81	67.30±0.91	67.86±0.84	68.63±1.09
40	87.52±0.82	86.65±0.82	85.52±0.81	88.39±0.48	88.31±1.09
50	95.58±0.61	94.44±0.81	95.31±0.84	94.00±0.65	94.03±0.49
60	98.74±0.64	98.48±1.01	97.79±0.92	97.35±0.57	97.31±0.83

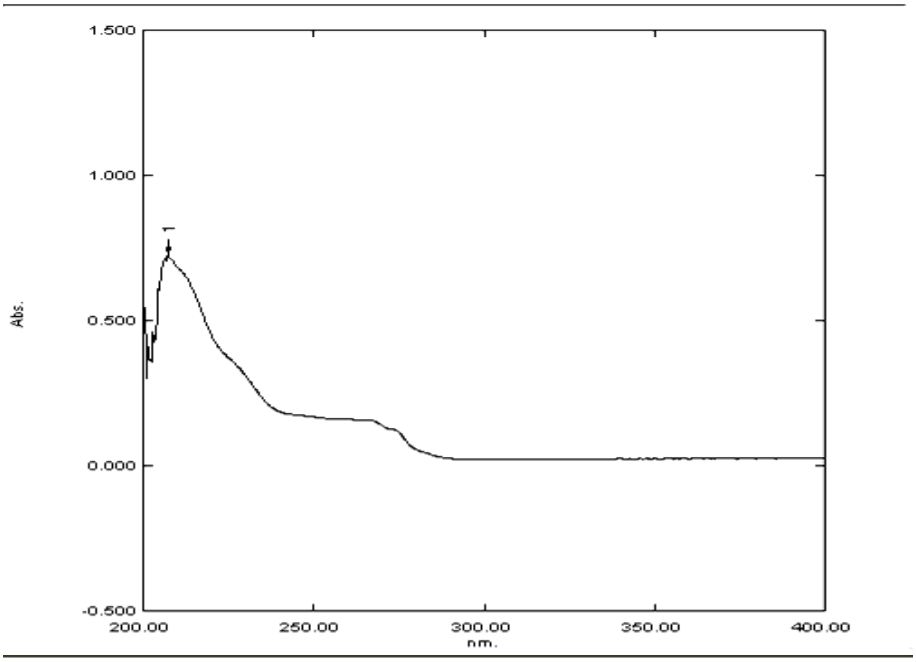


Figure: 5 Determination of λmax of pioglitazone hydrochloride

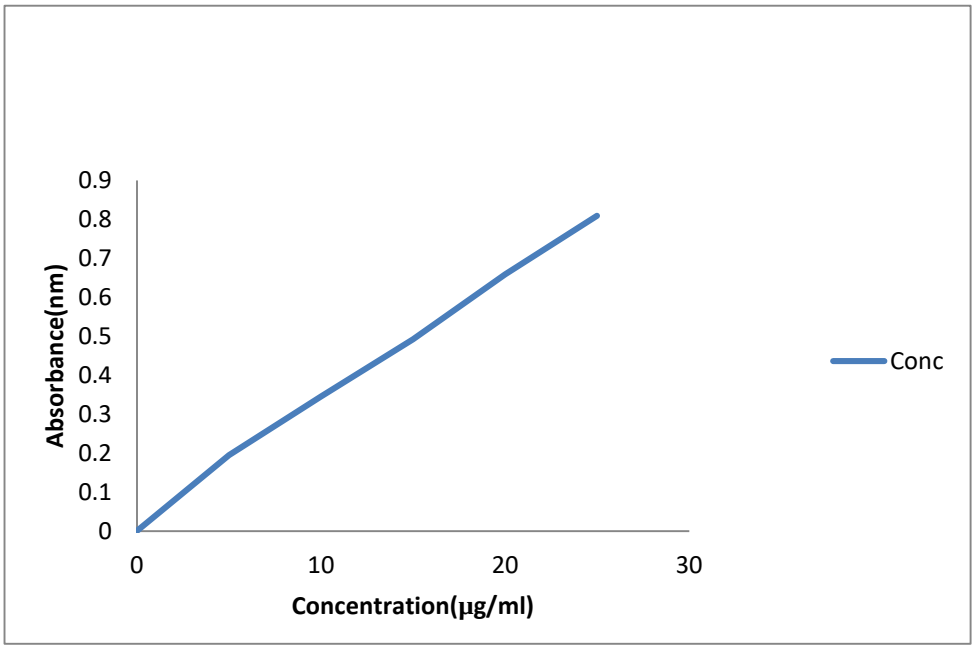


Figure: 6 Calibration curve of pioglitazone hydrochloride in phosphate buffer pH 7.4

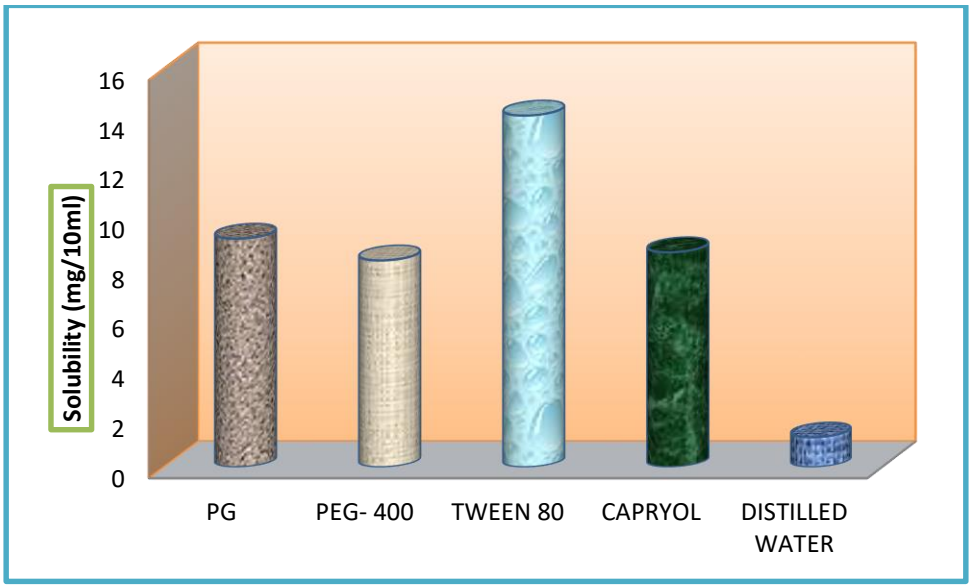


Figure :7 Solubility of pioglitazone hydrochloride in various non-volatile liquid vehicles

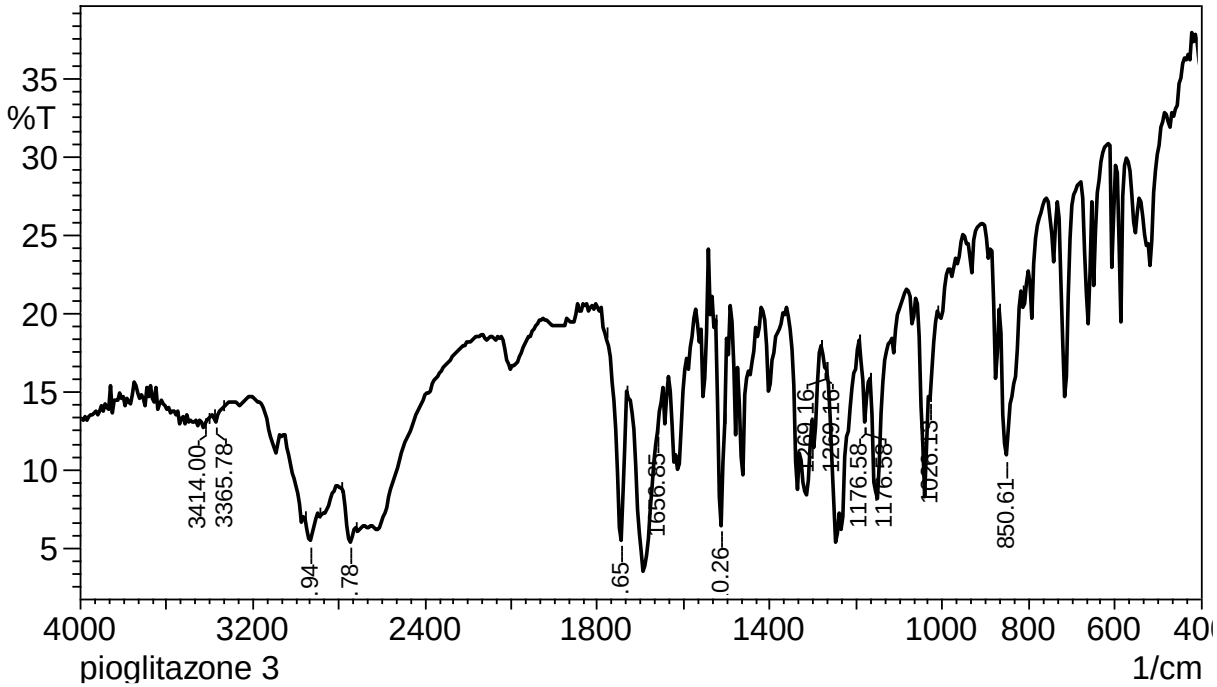


Figure: 8a FT-IR spectrum of pioglitazone hydrochloride

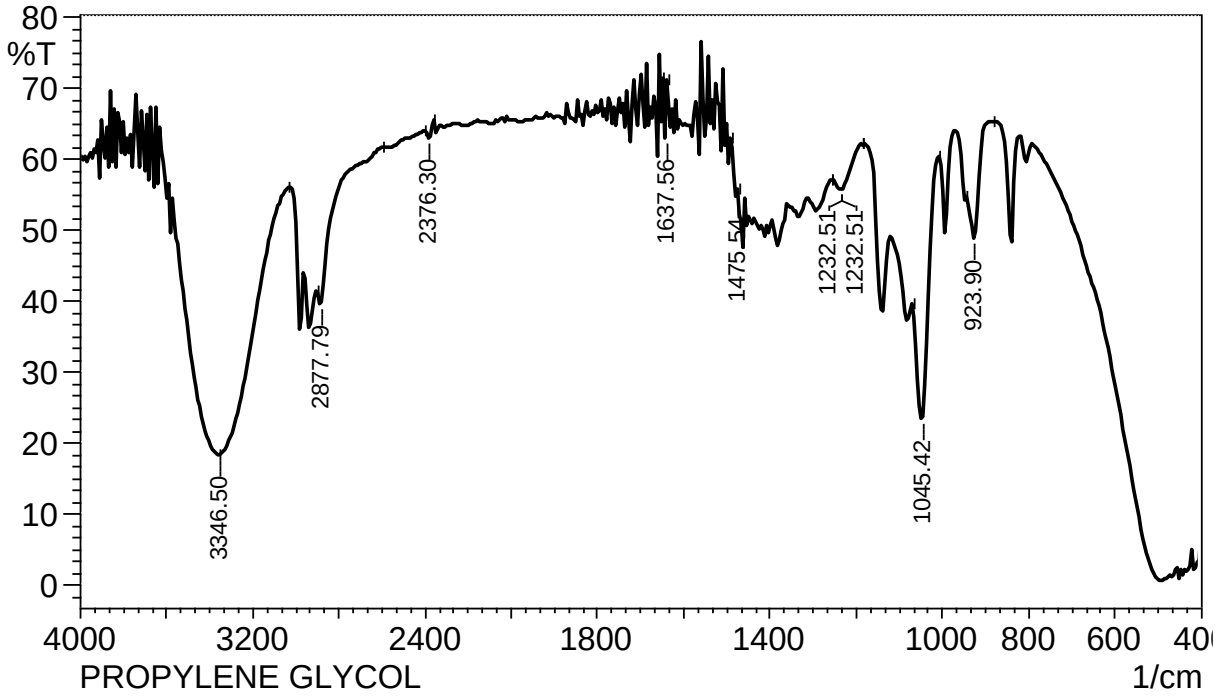


Figure: 8b FT-IR spectrum of propylene glycol

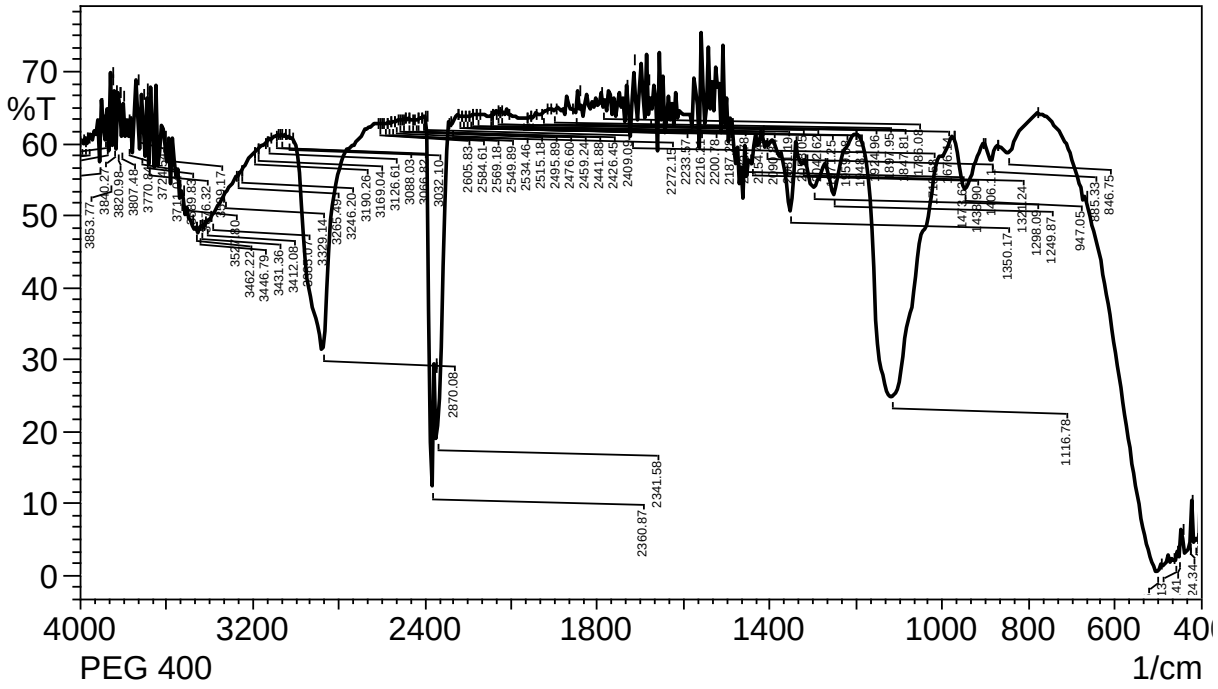


Figure: 8c FT-IR spectrum of polyethylene glycol-400

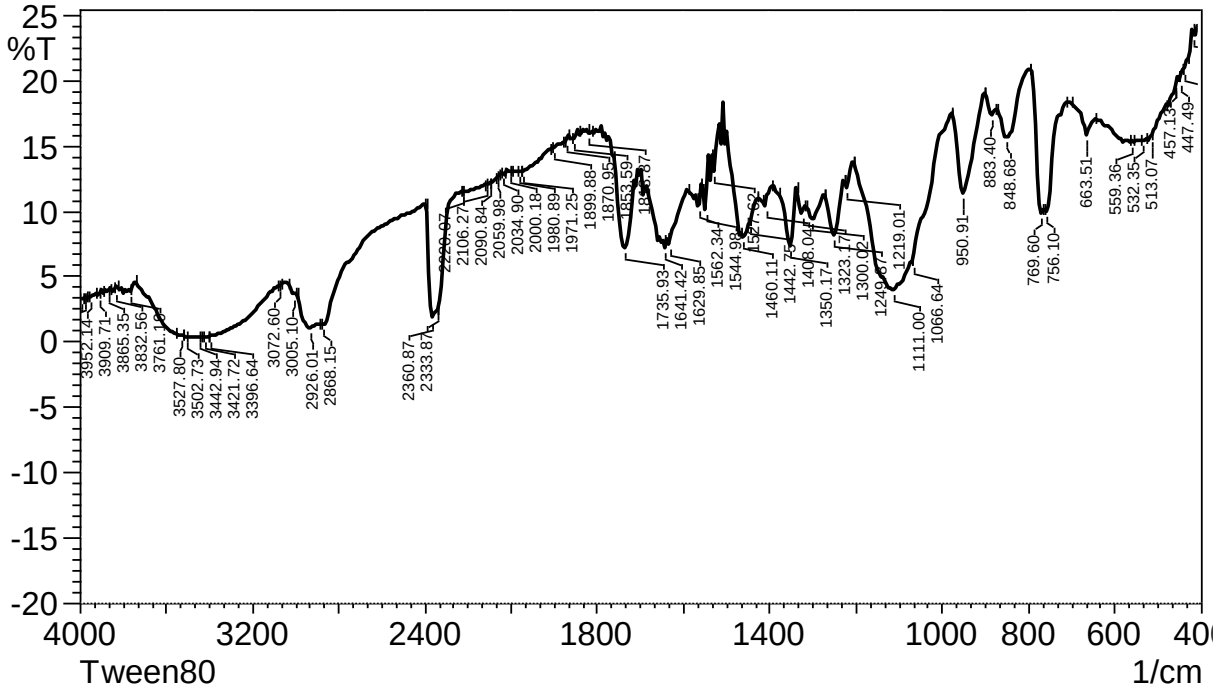


Figure: 8d FT-IR spectrum of tween 80

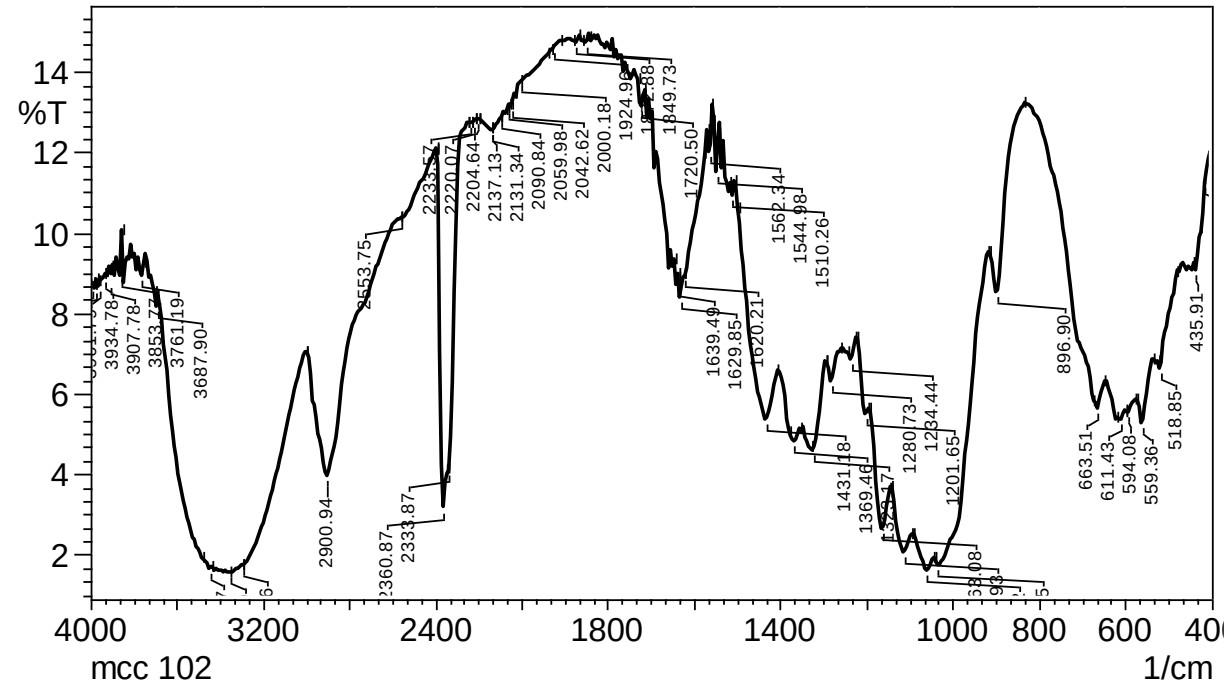


Figure:8e FT-IR spectrum of microcrystalline cellulose

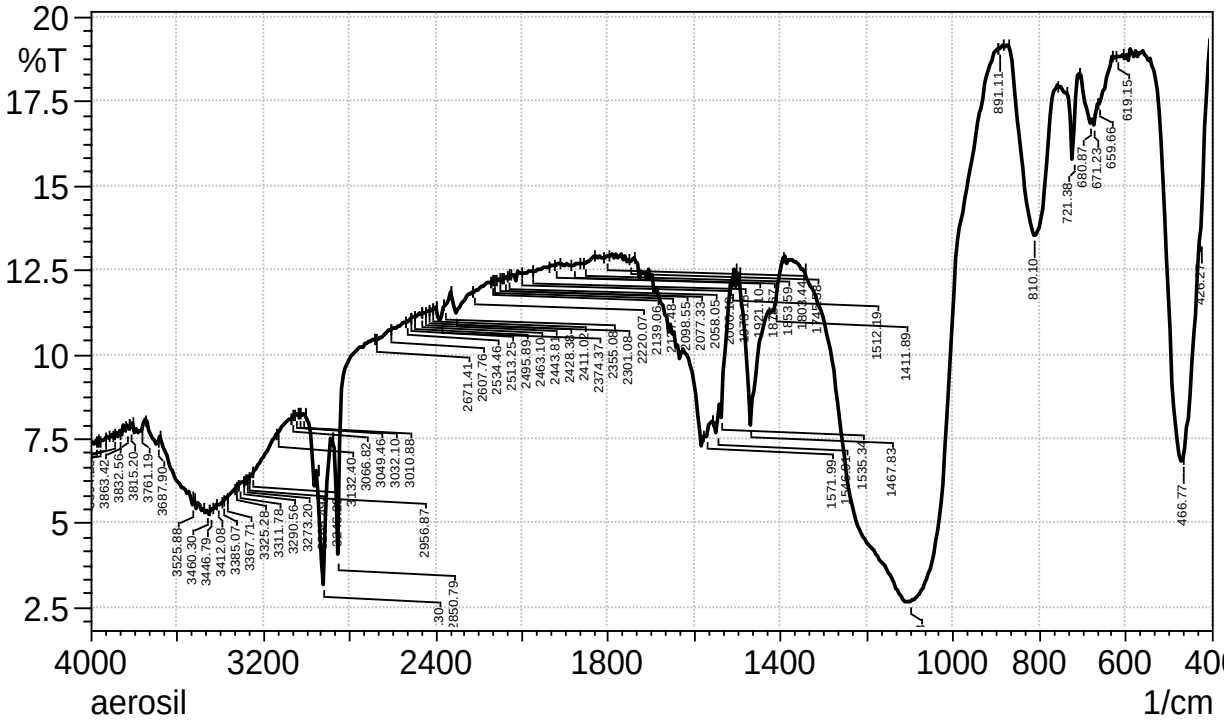


Figure: 8f FT-IR spectrum of Aerosil

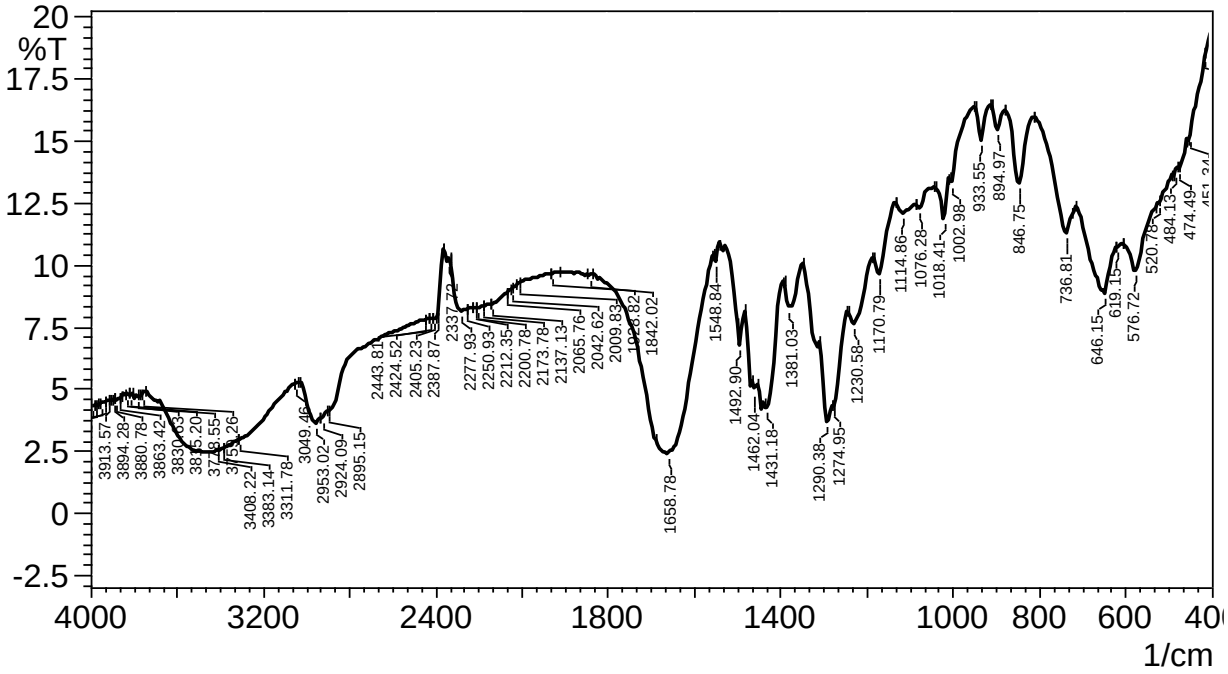


Figure: 8g FT-IT spectrum of crospovidone

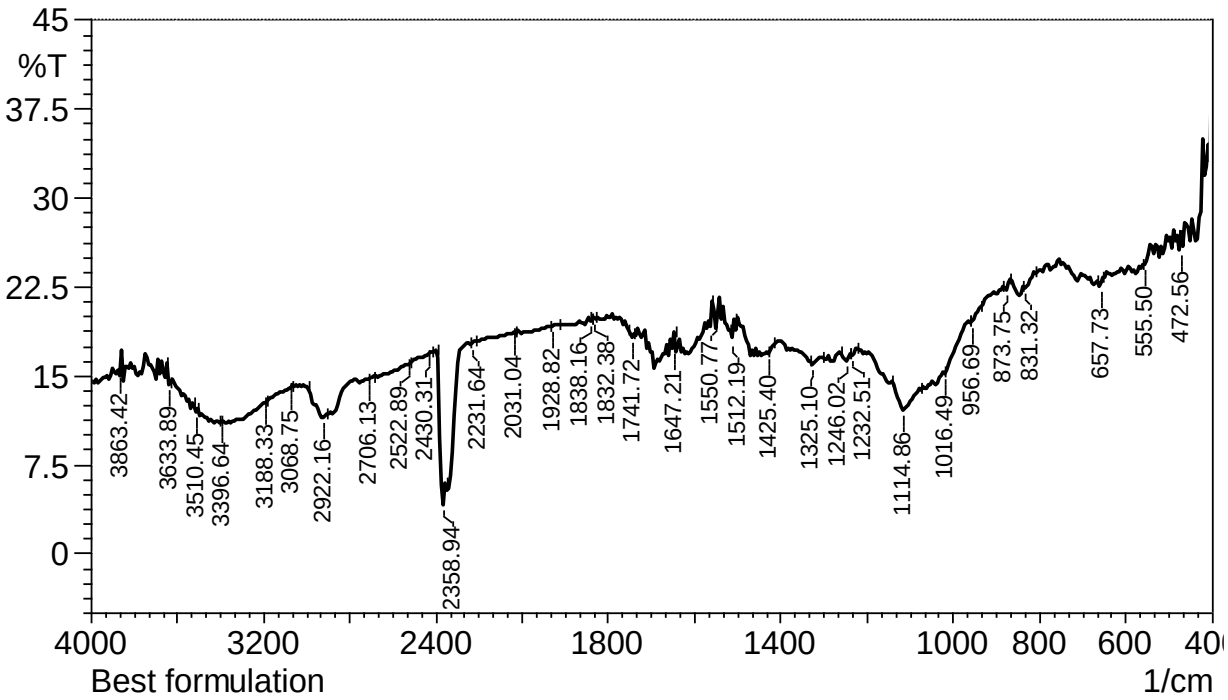


Figure: 8h FT-IR spectrum of Drug + Tween 80+ Microcrystalline cellulose + Aerosil

Figure 9a:DSC thermogram of pioglitazone hydrochloride

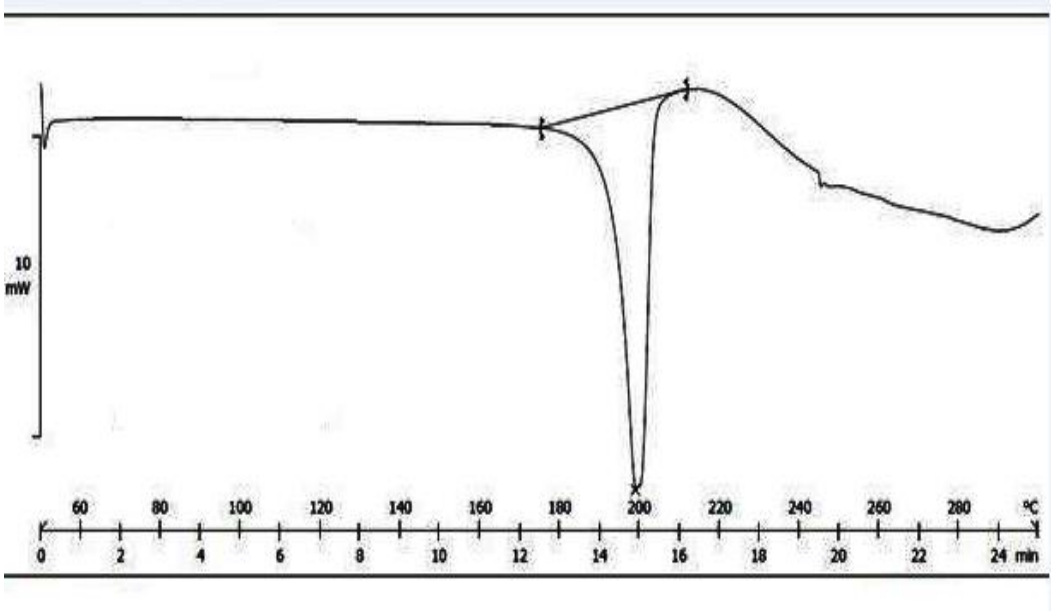


Figure 9b: DSC thermogram of liquisolid formulation

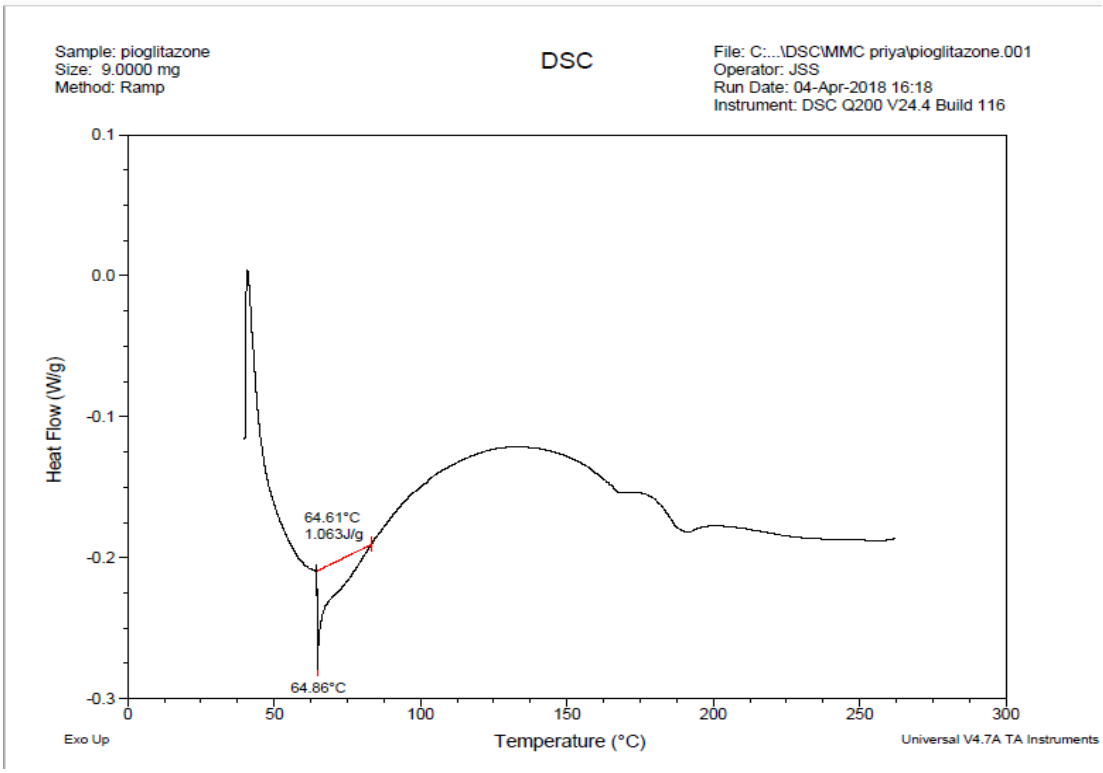


Figure 10a: Powder X- ray diffraction studies for pioglitazone hydrochloride

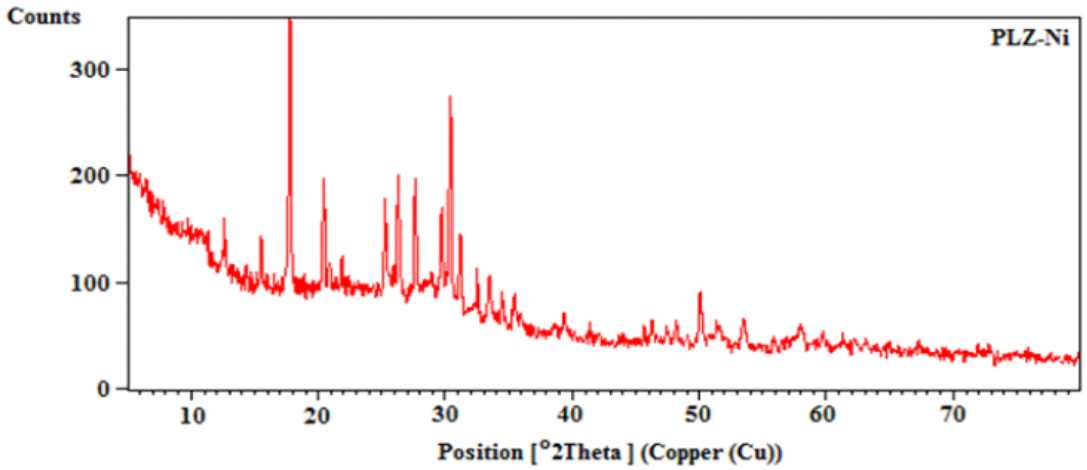
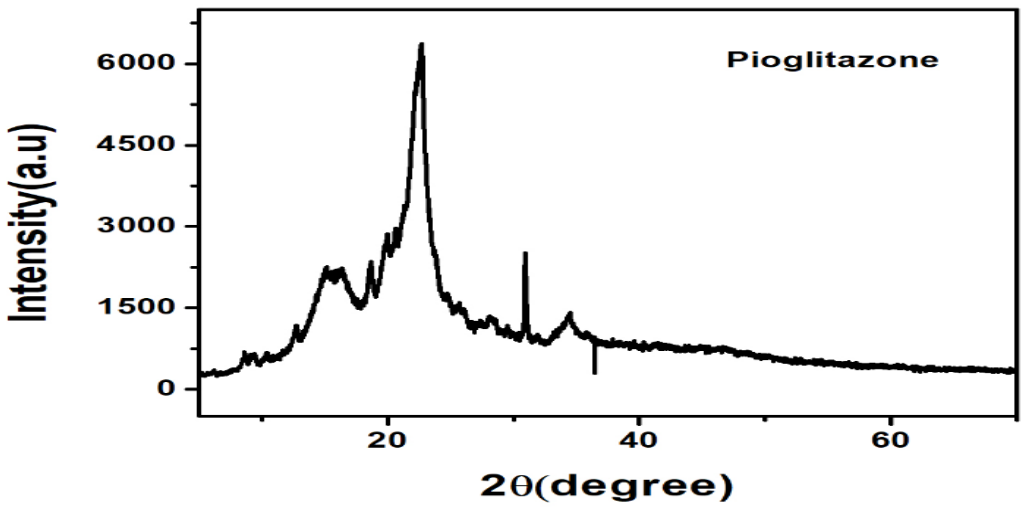


Figure 10 b : Powder X- ray diffraction studies for liquisolid formulation



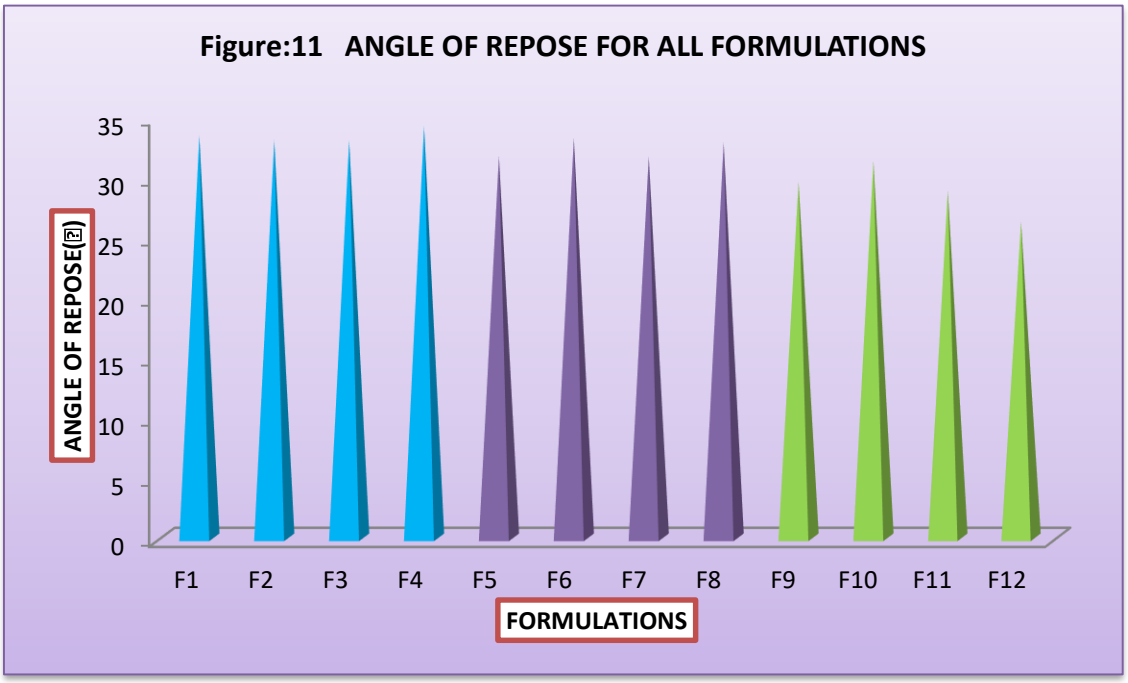


Figure:11 ANGLE OF REPOSE FOR ALL FORMULATIONS
ANGLE OF REPOSE(θ)
35
30
25
20
15
10
5
0
F1
F2
F3
F4
F5
F6
F7
F8
F9
F10
F11
F12
FORMULATIONS

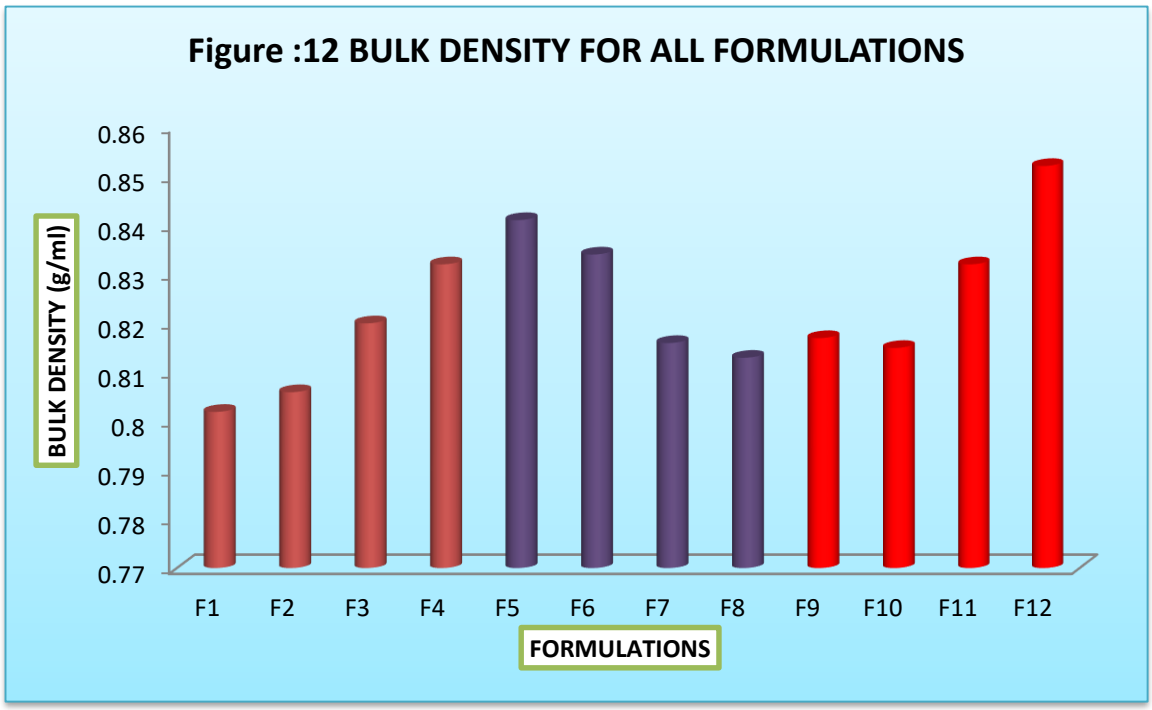


Figure :12 BULK DENSITY FOR ALL FORMULATIONS
BULK DENSITY (g/ml)
0.86
0.85
0.84
0.83
0.82
0.81
0.8
0.79
0.78
0.77
F1
F2
F3
F4
F5
F6
F7
F8
F9
F10
F11
F12
FORMULATIONS

Figure:13 TAPPED DENSITY FOR ALL FORMULATIONS

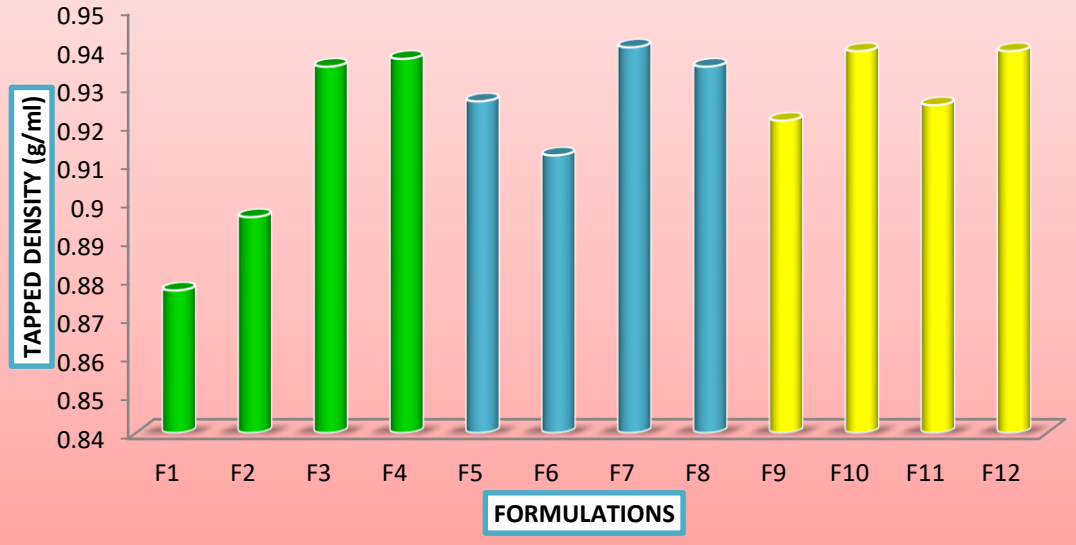


Figure:14 CARR'S INDEX FOR ALL FORMULATIONS

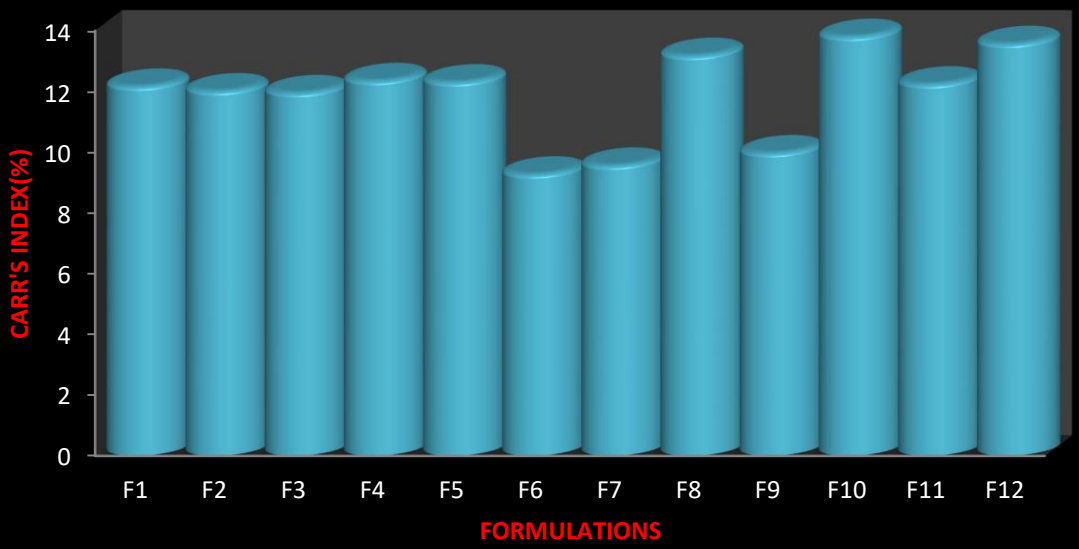


Figure:15 HAUSNER'S RATIO FOR ALL FORMULATIONS

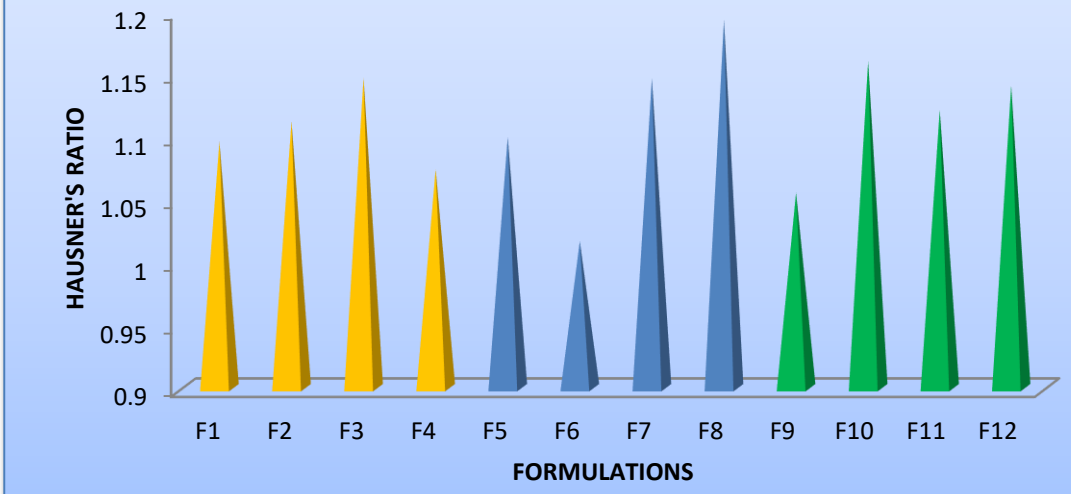
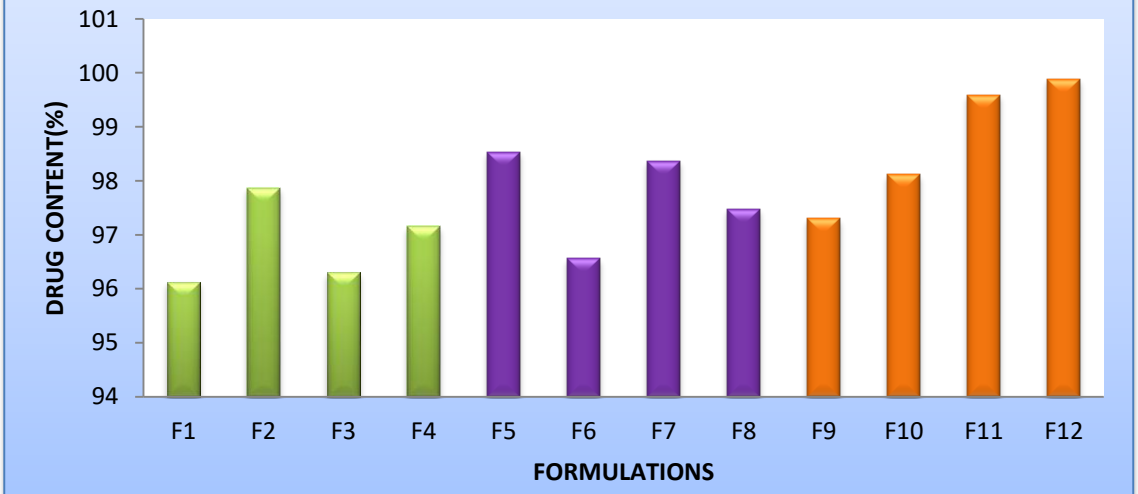


Figure:16 DRUG CONTENT FOR ALL FORMULATIONS



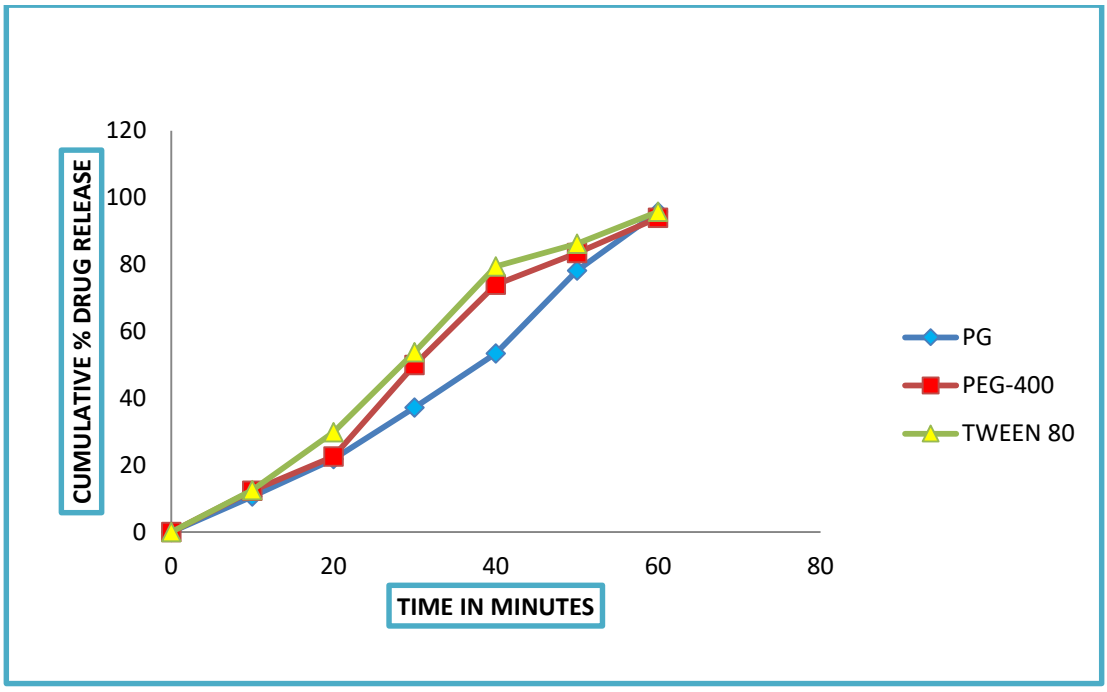


Figure :17a *in vitro* release profile of liquisolid tablets of pioglitazone hydrochloride [MCC:SILICA(5:1)]

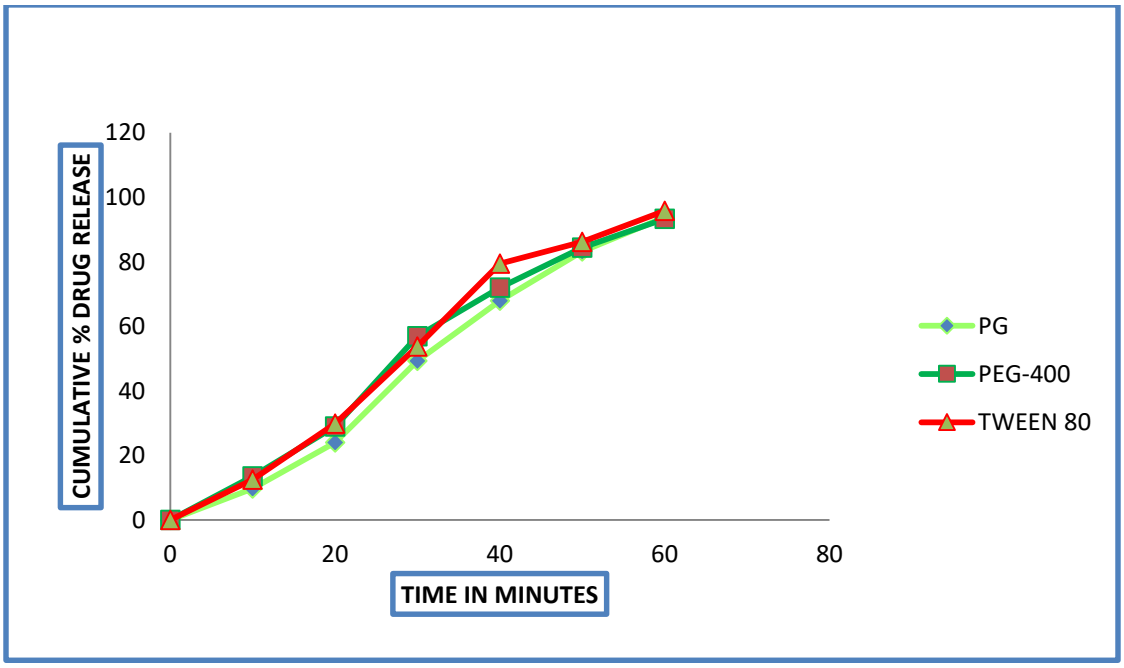


Figure :17b *in vitro* release profile of liquisolid tablets of pioglitazone hydrochloride [MCC:SILICA(10:1)]

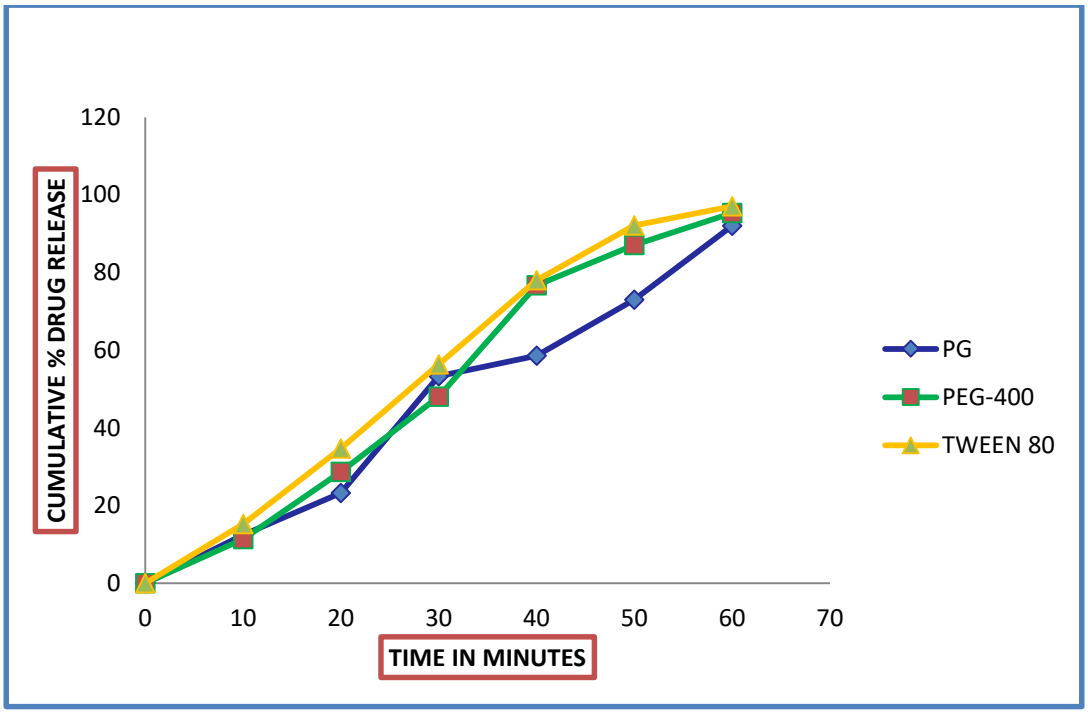


Figure : 17c *in vitro* release profile of liquisolid tablets of pioglitazone hydrochloride [MCC:SILICA(15:1)]

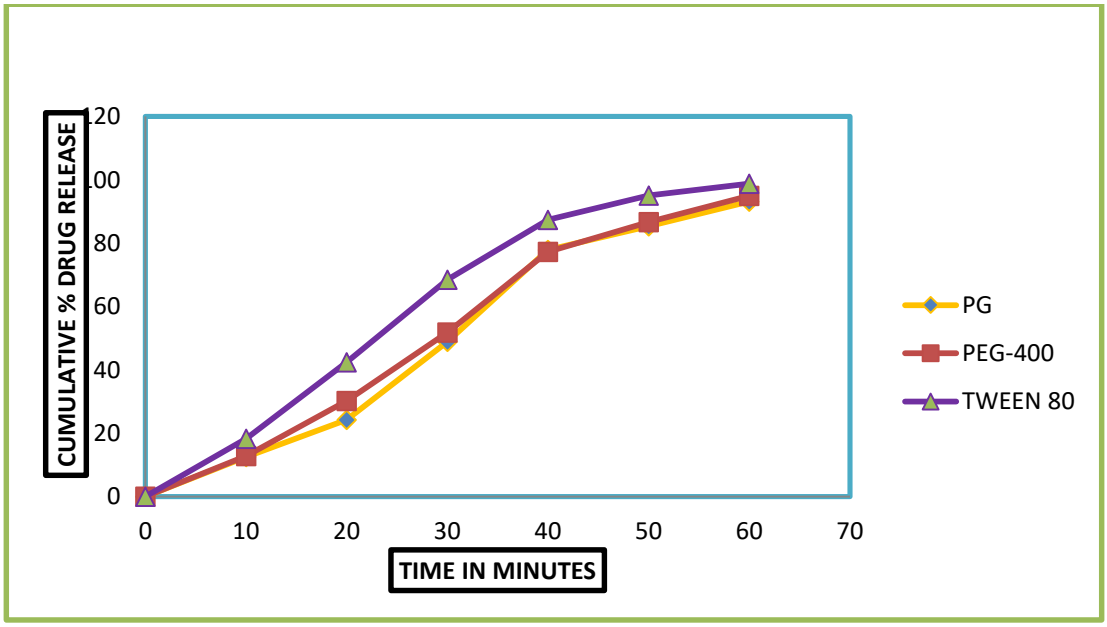


Figure :17d *in vitro* release profile of liquisolid tablets of pioglitazone hydrochloride [MCC:SILICA(20:1)]

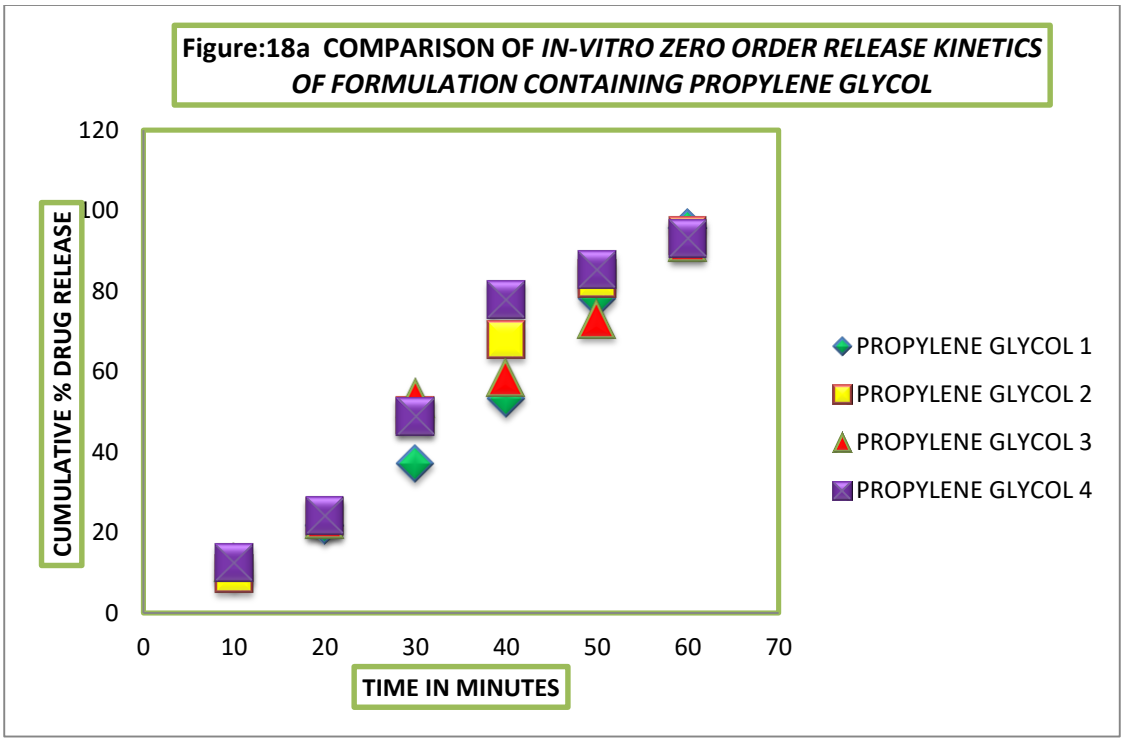


Figure:18a COMPARISON OF IN-VITRO ZERO ORDER RELEASE KINETICS OF FORMULATION CONTAINING PROPYLENE GLYCOL
CUMULATIVE % DRUG RELEASE
120
100
80
60
40
20
0
0
10
20
30
40
50
60
70
TIME IN MINUTES
PROPYLENE GLYCOL 1
PROPYLENE GLYCOL 2
PROPYLENE GLYCOL 3
PROPYLENE GLYCOL 4

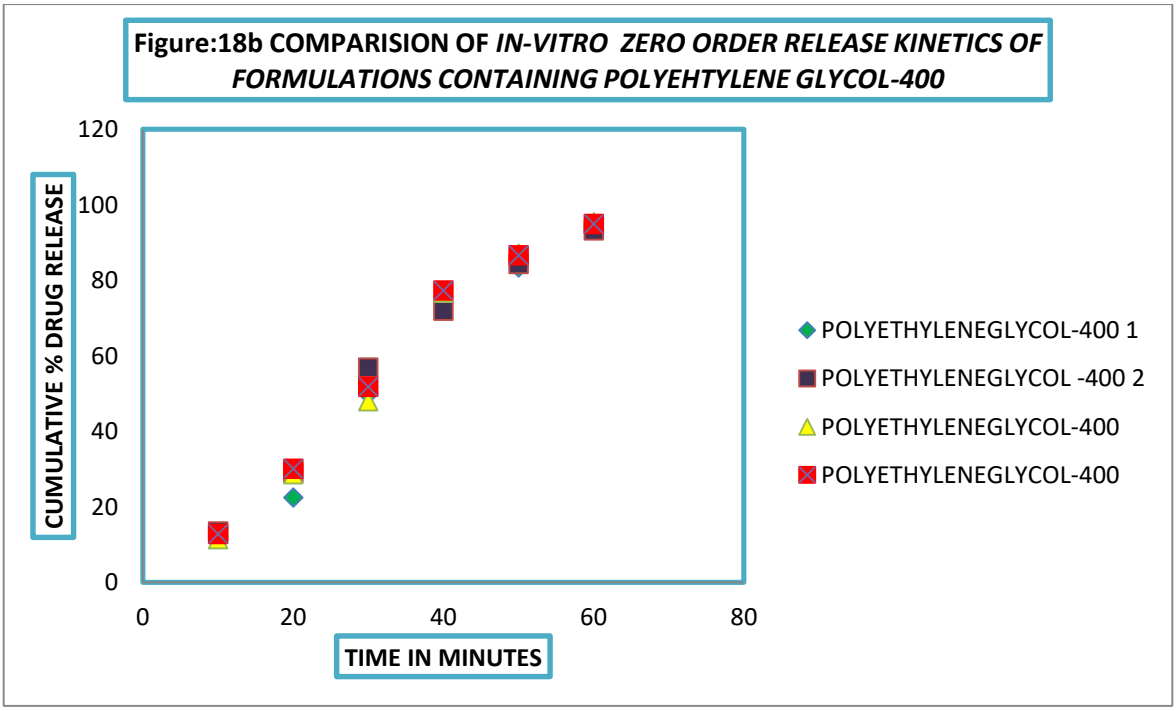


Figure:18b COMPARISION OF IN-VITRO ZERO ORDER RELEASE KINETICS OF FORMULATIONS CONTAINING POLYEHTYLENE GLYCOL-400
CUMULATIVE % DRUG RELEASE
120
100
80
60
40
20
0
0
20
40
60
80
TIME IN MINUTES
POLYETHYLENEGLYCOL-400 1
POLYETHYLENEGLYCOL -400 2
POLYETHYLENEGLYCOL-400
POLYETHYLENEGLYCOL-400

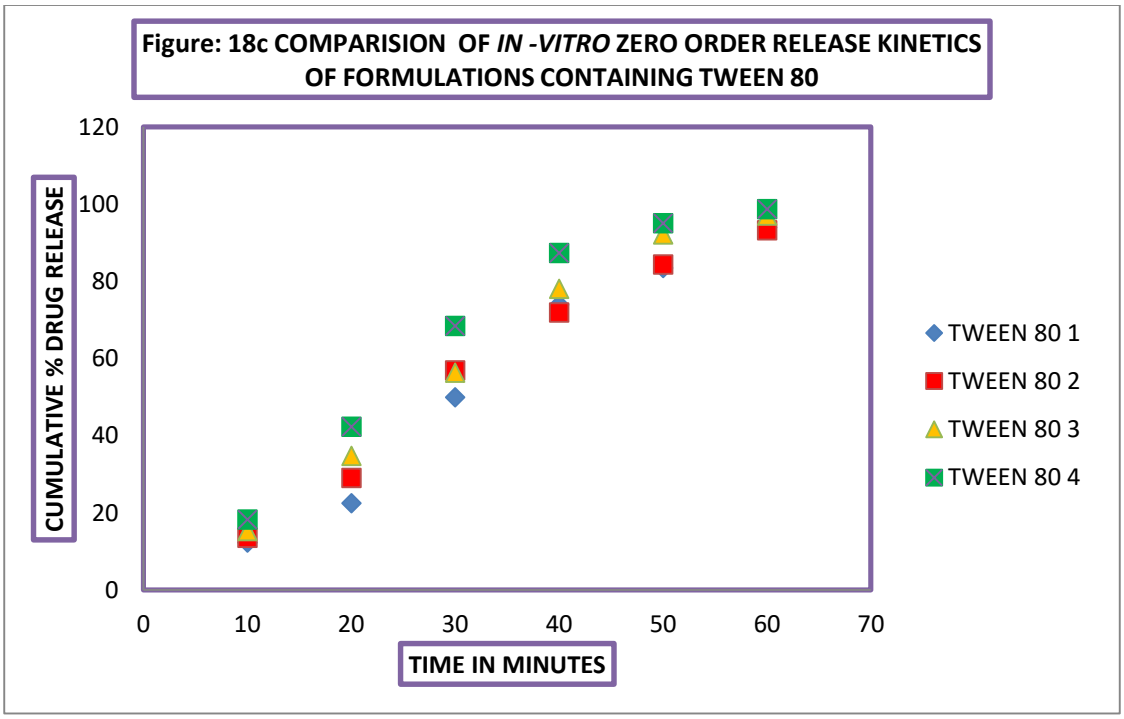


Figure: 18c COMPARISION OF *IN -VITRO* ZERO ORDER RELEASE KINETICS OF FORMULATIONS CONTAINING TWEEN 80
CUMULATIVE % DRUG RELEASE
120
100
80
60
40
20
0
0
10
20
30
40
50
60
70
TIME IN MINUTES
TWEEN 80 1
TWEEN 80 2
TWEEN 80 3
TWEEN 80 4

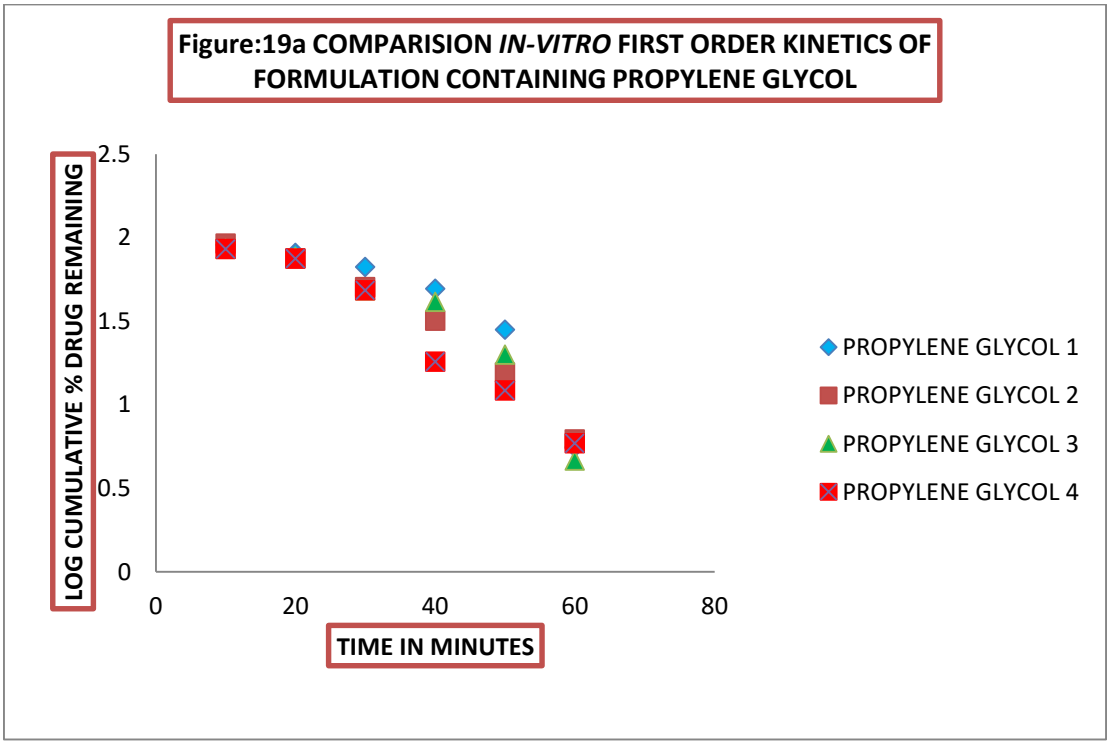


Figure:19a COMPARISION *IN-VITRO* FIRST ORDER KINETICS OF FORMULATION CONTAINING PROPYLENE GLYCOL
LOG CUMULATIVE % DRUG REMAINING
2.5
2
1.5
1
0.5
0
0
20
40
60
80
TIME IN MINUTES
PROPYLENE GLYCOL 1
PROPYLENE GLYCOL 2
PROPYLENE GLYCOL 3
PROPYLENE GLYCOL 4

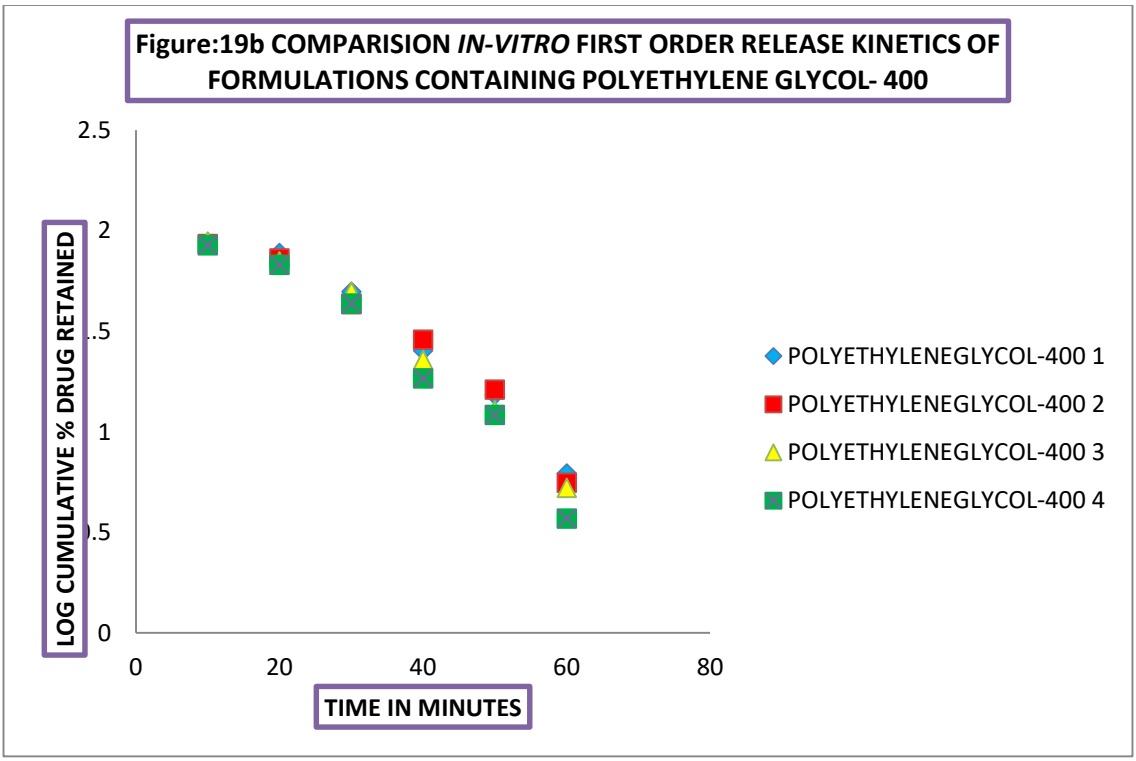


Figure:19b COMPARISION *IN-VITRO* FIRST ORDER RELEASE KINETICS OF FORMULATIONS CONTAINING POLYETHYLENE GLYCOL- 400
LOG CUMULATIVE % DRUG RETAINED
2.5
2
1
0
0
20
40
60
80
TIME IN MINUTES
POLYETHYLENEGLYCOL-400 1
POLYETHYLENEGLYCOL-400 2
POLYETHYLENEGLYCOL-400 3
POLYETHYLENEGLYCOL-400 4

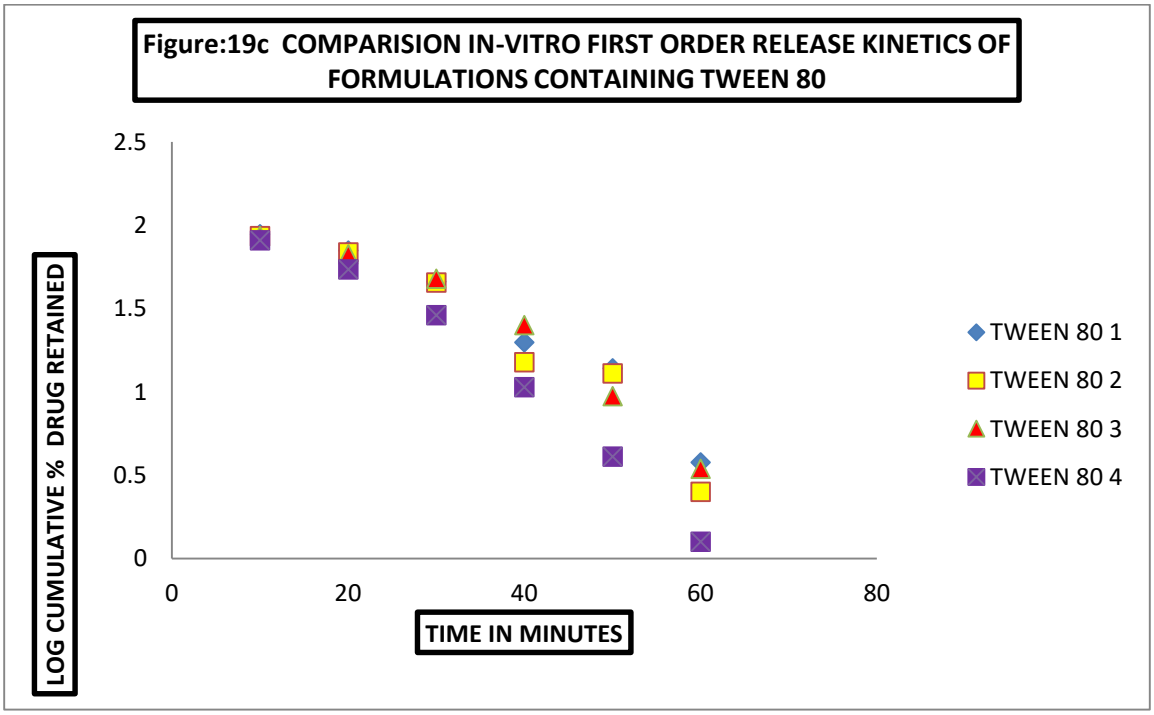


Figure:19c COMPARISION IN-VITRO FIRST ORDER RELEASE KINETICS OF FORMULATIONS CONTAINING TWEEN 80
LOG CUMULATIVE % DRUG RETAINED
2.5
2
1.5
1
0.5
0
0
20
40
60
80
TIME IN MINUTES
TWEEN 80 1
TWEEN 80 2
TWEEN 80 3
TWEEN 80 4

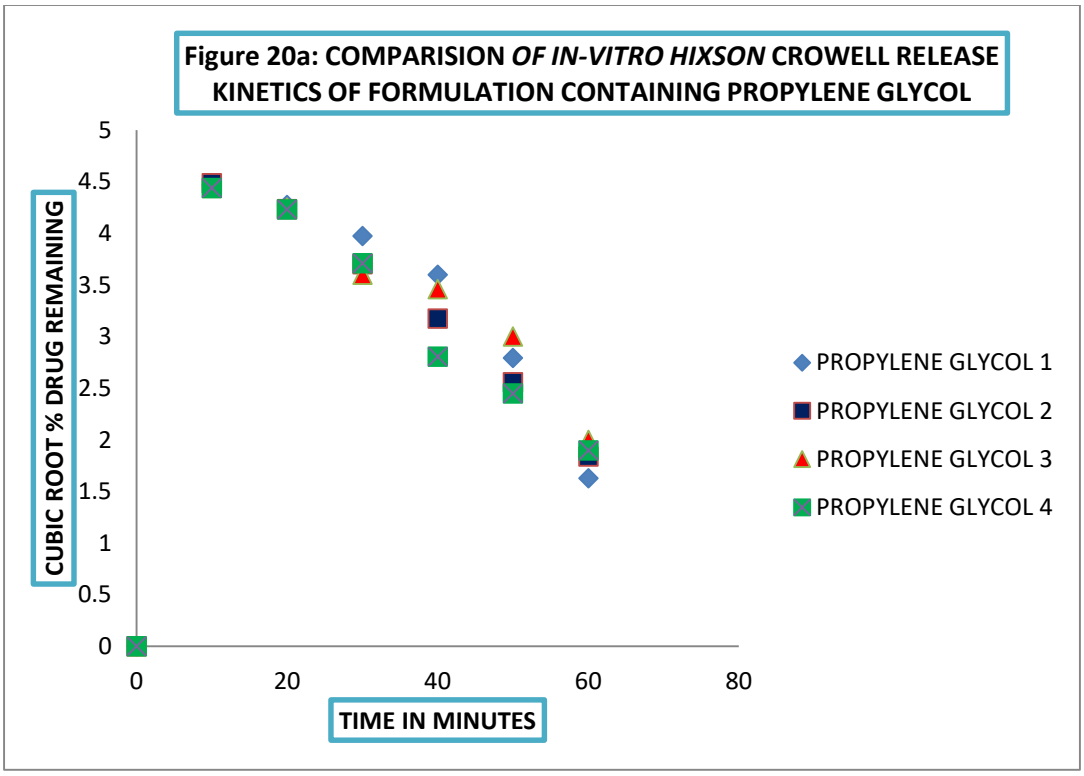


Figure 20a: COMPARISION *OF IN-VITRO HIXSON* CROWELL RELEASE KINETICS OF FORMULATION CONTAINING PROPYLENE GLYCOL
CUBIC ROOT % DRUG REMAINING
5
4.5
4
3.5
3
2.5
2
1.5
1
0.5
0
0
20
40
60
80
TIME IN MINUTES
PROPYLENE GLYCOL 1
PROPYLENE GLYCOL 2
PROPYLENE GLYCOL 3
PROPYLENE GLYCOL 4

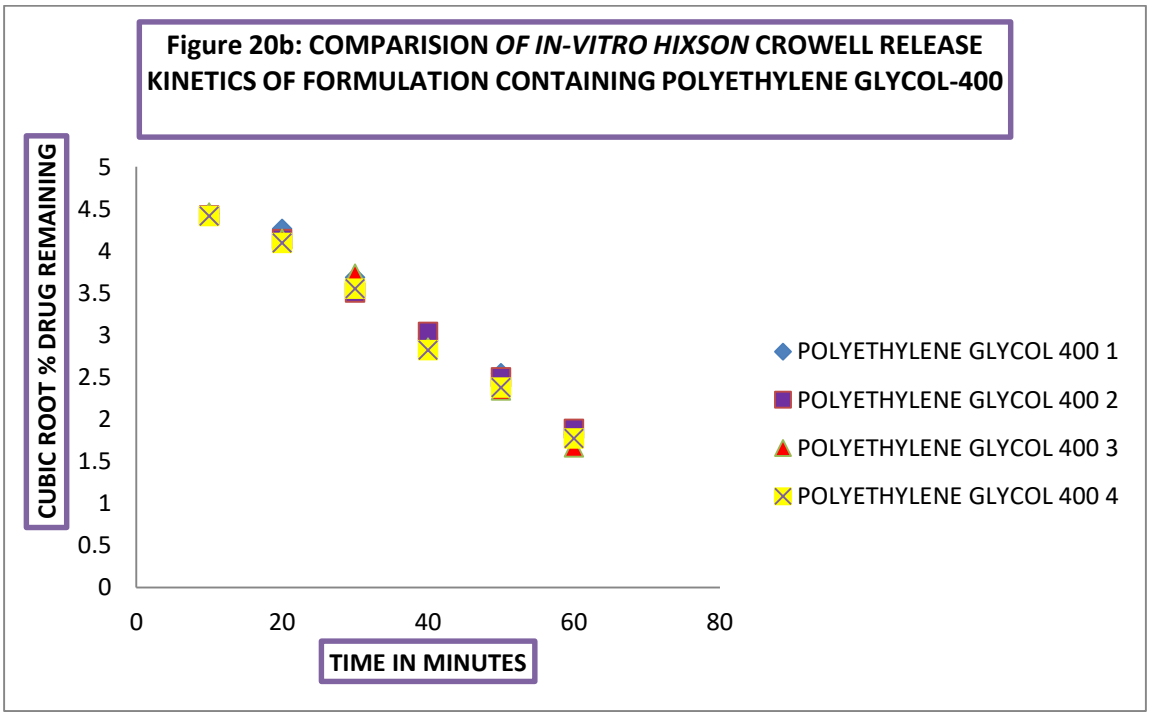


Figure 20b: COMPARISION *OF IN-VITRO HIXSON* CROWELL RELEASE KINETICS OF FORMULATION CONTAINING POLYETHYLENE GLYCOL-400
CUBIC ROOT % DRUG REMAINING
5
4.5
4
3.5
3
2.5
2
1.5
1
0.5
0
0
20
40
60
80
TIME IN MINUTES
POLYETHYLENE GLYCOL 400 1
POLYETHYLENE GLYCOL 400 2
POLYETHYLENE GLYCOL 400 3
POLYETHYLENE GLYCOL 400 4

Figure 20c: COMPARISION *OF IN-VITRO HIXSON* CROWELL RELEASE KINETICS OF FORMULATION CONTAINING TWEEN 80

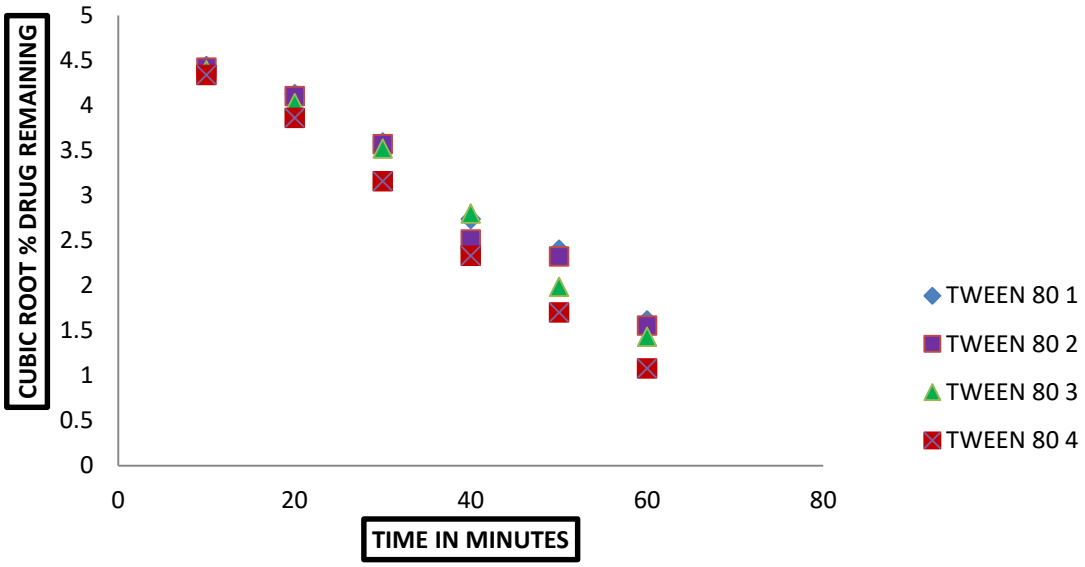


Figure 21a: COMPARISON OF *IN VITRO* HIGUCHI MODEL RELEASE KINETICS CONTAINING PROPYLENE GLYCOL

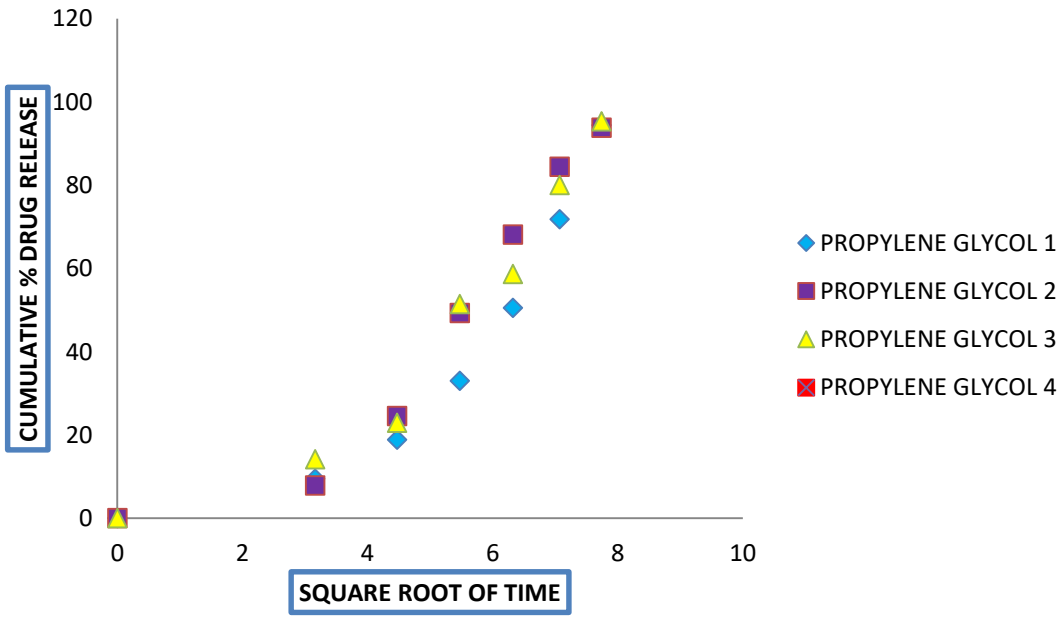


Figure 21b: COMPARISON *IN-VITRO* HIGUCHI MODEL RELEASE KINETICS OF FORMULATION CONTAINING POLYETHYLENE GLYCOL-400

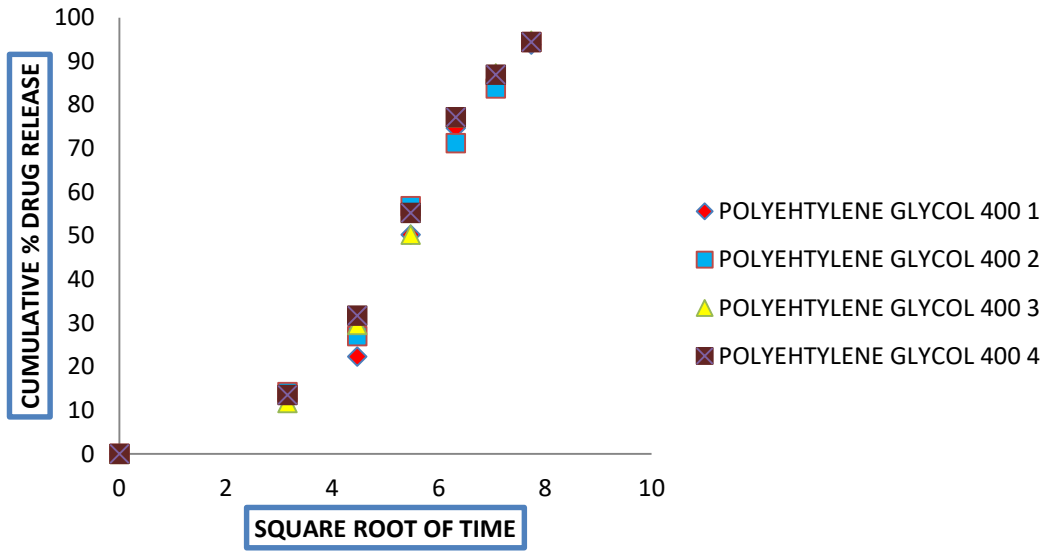


Figure 21c :COMPARISION OF *IN-VITRO* HIGUCHI MODEL RELEASE KINETICS OF FORMULATIONS CONTAINING TWEEN 80

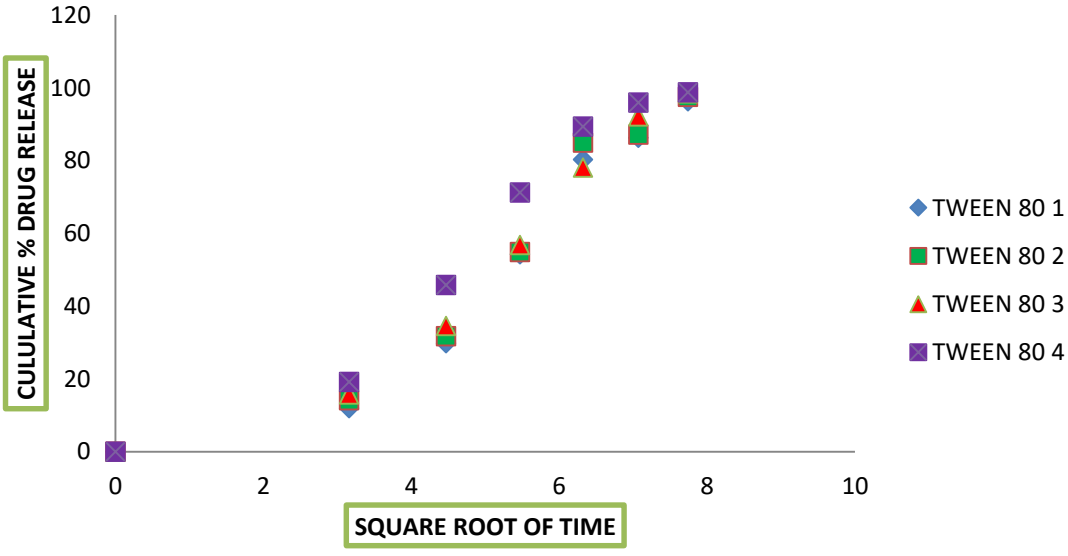


Figure 22a:COMPARISION OF *IN-VITRO* KORES MEYER-PEPPAS MODEL RELEASE KINETICS OF FORMULATION CONTAINING PROPYLENE GLYCOL

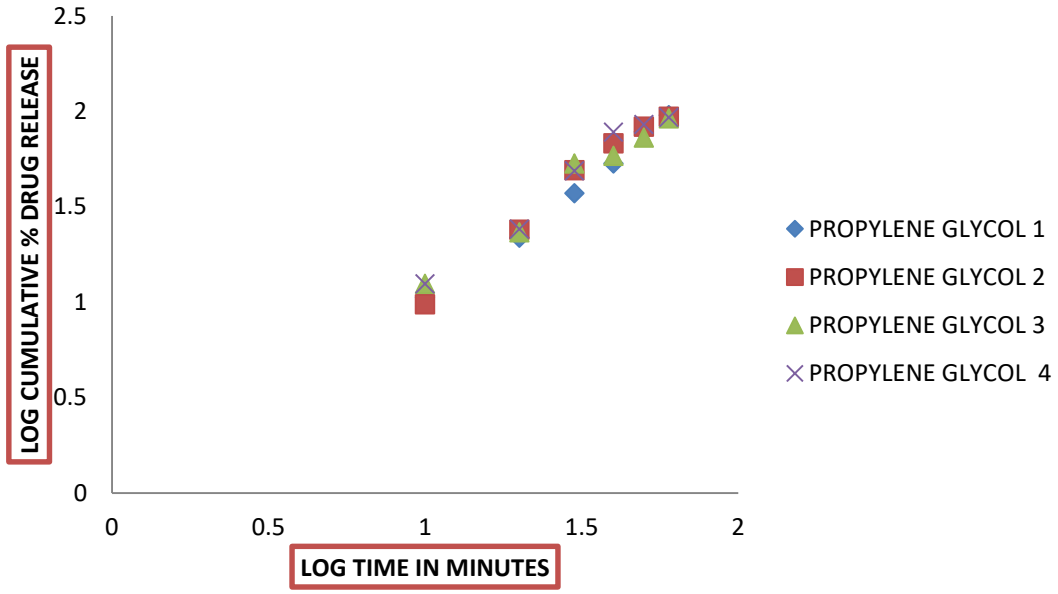
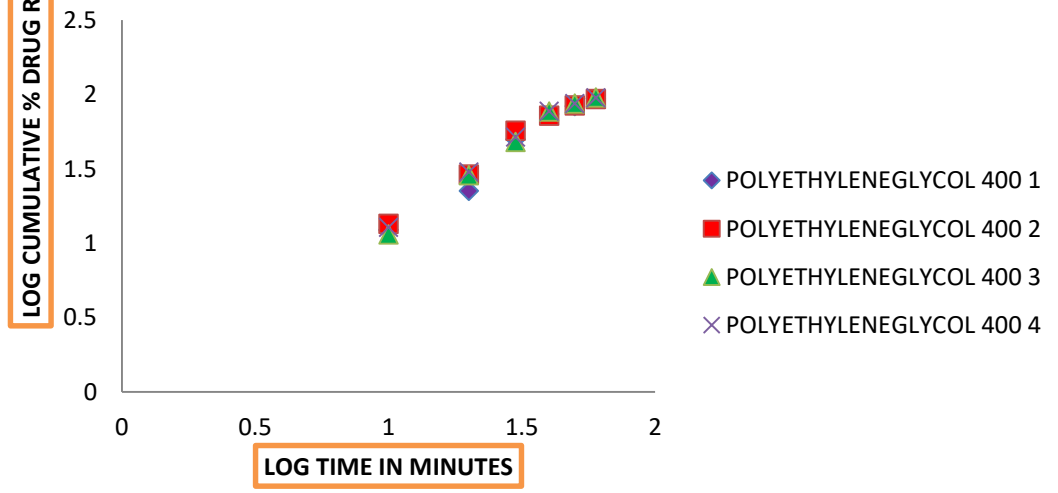


Figure 22b:COMPARISION OF *IN-VITRO* KORES MEYER-PEPPAS MODEL RELEASE KINETICS OF FORMULATION CONTAINING POLYEHTYLENE GLYCOL-400



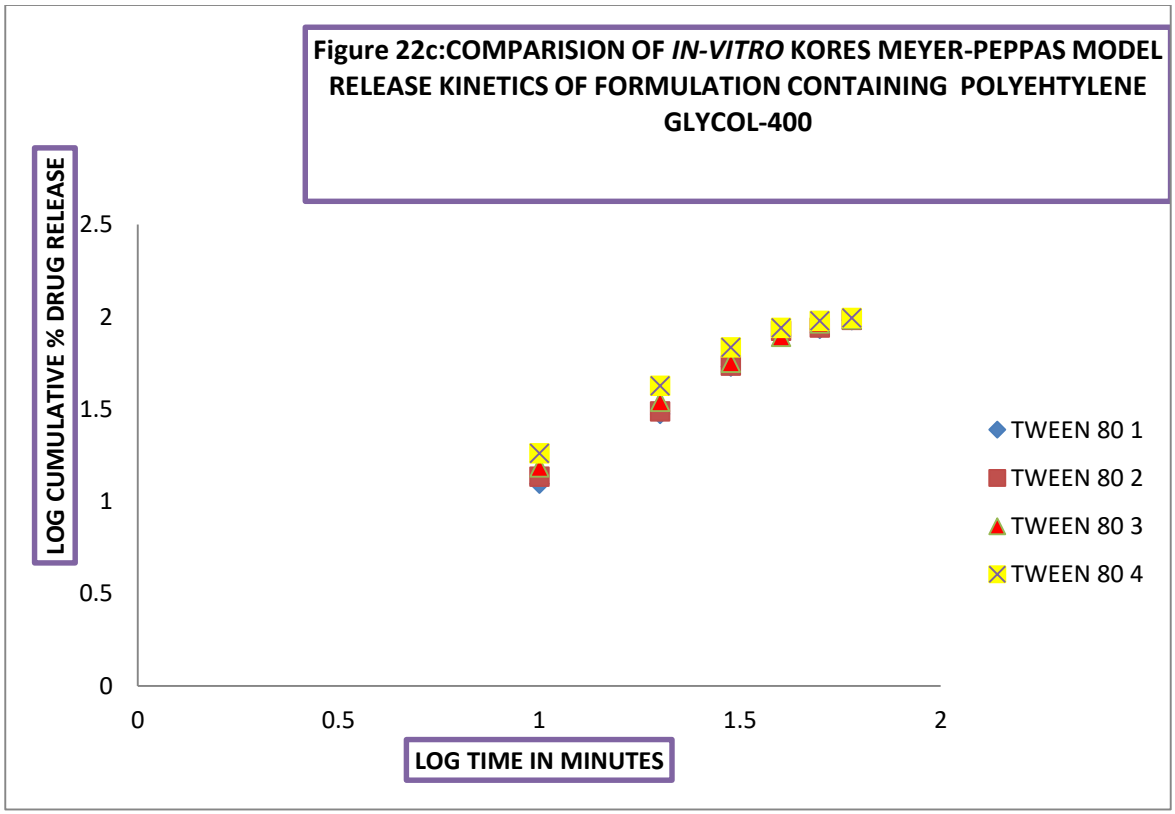


Figure 22c:COMPARISION OF *IN-VITRO* KORES MEYER-PEPPAS MODEL RELEASE KINETICS OF FORMULATION CONTAINING POLYEHTYLENE GLYCOL-400
LOG CUMULATIVE % DRUG RELEASE
2.5
2
1.5
1
0.5
0
0
0.5
1
1.5
2
LOG TIME IN MINUTES
TWEEN 80 1
TWEEN 80 2
TWEEN 80 3
TWEEN 80 4

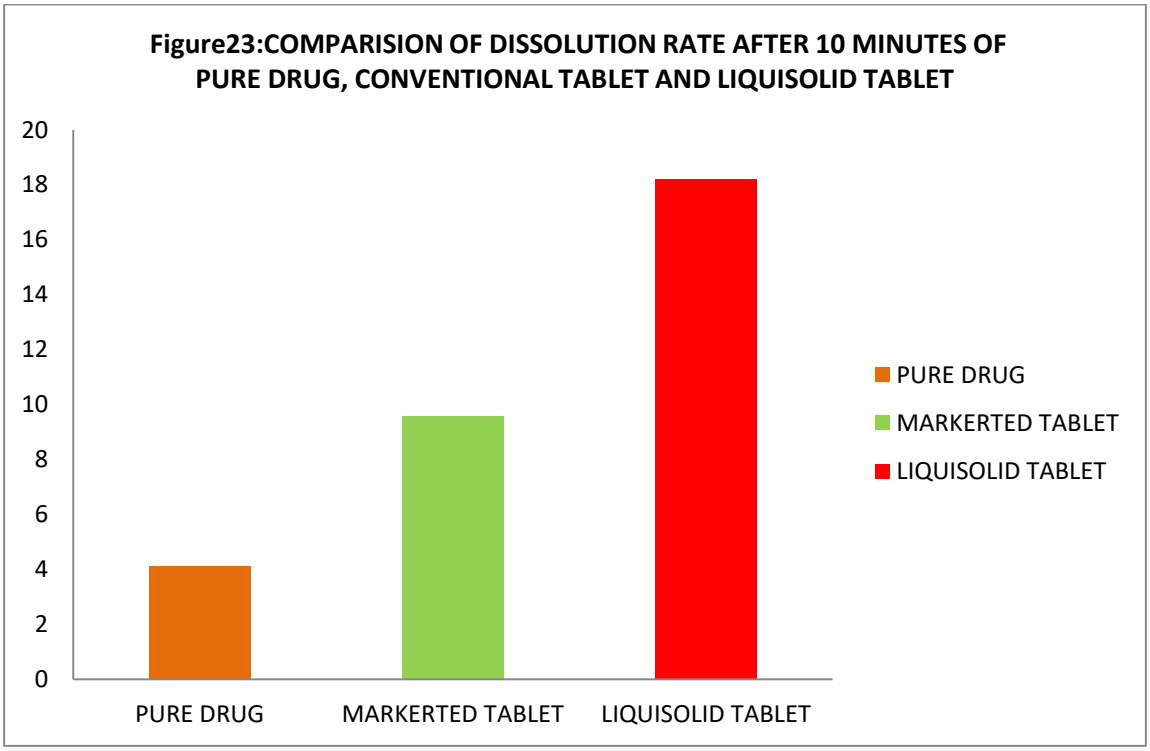


Figure23:COMPARISION OF DISSOLUTION RATE AFTER 10 MINUTES OF PURE DRUG, CONVENTIONAL TABLET AND LIQUISOLID TABLET
20
18
16
14
12
10
8
6
4
2
0
PURE DRUG
MARKERTED TABLET
LIQUISOLID TABLET
PURE DRUG
MARKERTED TABLET
LIQUISOLID TABLET

Figure 24:COMPARISION OF *IN-VITRO RELEASE STUDIES LIQUISOLID FORMULATION WITH PURE DRUG, AND CONVENTIONAL TABLET*

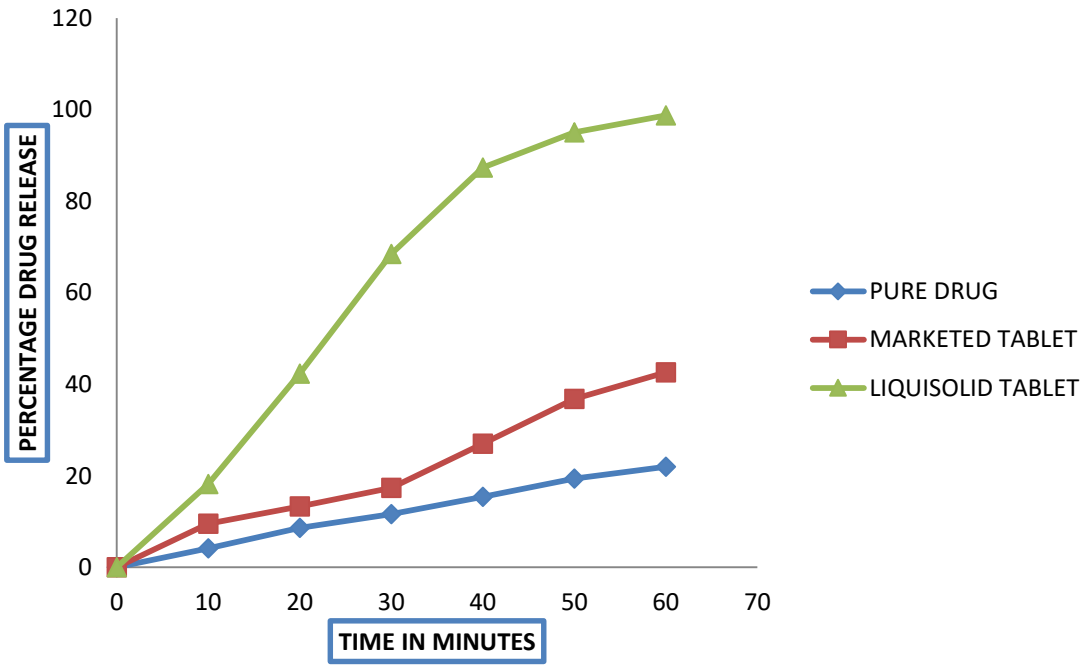
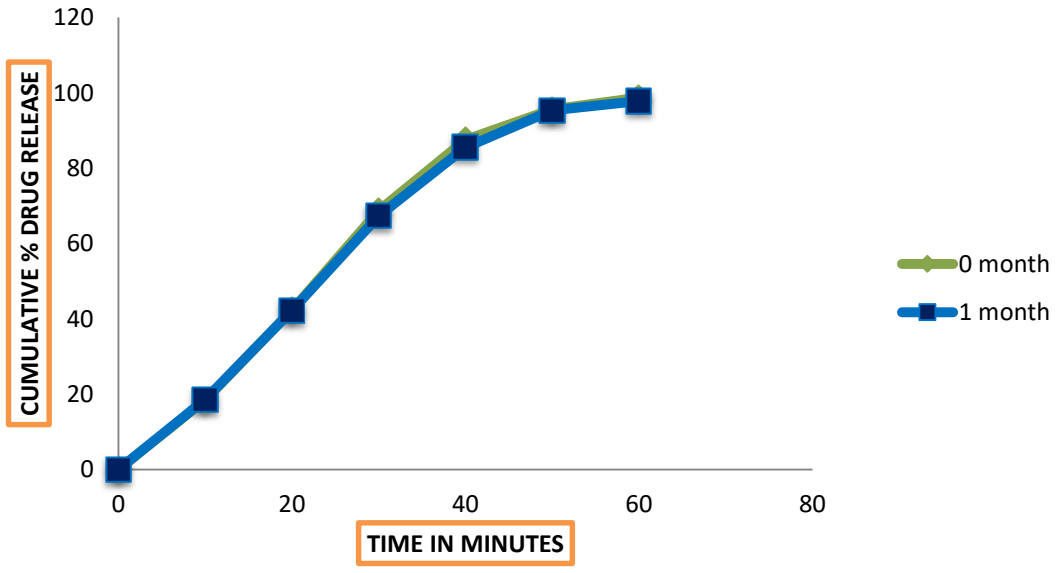


Figure 25:COMPARISON OF *IN-VITRO* DISSOLUTION PROFILE (12) OF 0 MONTH 1 MONTH (STORED AT 40C±2 RH 75 % ±5%)



CHAPTER-10

SUMMARY AND CONCLUSION

CHAPTER – X

SUMMARY AND CONCLUSION

The purpose of the study was to formulate liquisolid tablets of Pioglitazone hydrochloride to improve the solubility and dissolution rate. The λmax of Pioglitazone hydrochloride was found to be 234nm in phosphate buffer ph 7.4. The Pioglitazone hydrochloride obeys Beer's law within the concentration range of 5-25 (µg/ml). The solubility studies were observed that the Pioglitazone hydrochloride have highest solubility in Tween 80 compared to other non-volatile liquid vehicles. FT-IR showed that there was no interaction between the drug and excipients. The DSC thermogram of Pioglitazone hydrochloride and liquisolid compacts, the sharpendothermic peak of pure drug appeared at 187oC, whereas no such peak was observed in liquisolid formulation, which indicates that Pioglitazone hydrochloride was molecularly dispersed and in an amorphous form.

Flowable liquid retention potential (Φ-value) was used to formulate liquisolid tablets of Pioglitazone hydrochloride. The twelve formulations were prepared using different concentration of drug in liquid medication, and different ratio of microcrystalline cellulose & aerosil 200 and crospovidone. The directly compressed tablets were prepared using microcrystalline cellulose and aerosil 200 and crospovidone, without addition of non-volatile liquid vehicle.

The results of precompression studies which indicates that the prepared powder blend of all the formulations possess good flow properties. The postcompression evaluations such as hardness, thickness, weight variation, friability, drug content and

disintegration test of all the formulated liquisolid tablets were within the acceptable limits. *In vitro* dissolution studies of all the formulations showed immediate release of drug. Among 12 formulations F12 was selected as a best formulationwhich had the better release of drug (98.74%) and subjected to further studies.

The *in vitro* release studies revealed that the liquisolid tablets showed a faster drug release compared to the pure drug and directly compressed tablets. The results of the powder X- ray diffraction studies proved that the crystallinity of pure drug was remarkably reduced in the best formulation.

The dissolution rate (D_R) in 10 min, increased in linear manner with increasing ratio of drug: Tween 80. The selected formulation showed higher release profile than the pure drug and directly compressed tablets. The selected formulation was found to be stable under the storage condition

CONCLUSION

The liquisolid tablet technique can be effective way for dissolution rate improvement of water insoluble drugs such as Pioglitazone hydrochloride. Tween 80 was used as a liquid vehicle. The liquid vehicle plays a contributing role in improving the dissolution profiles of a water insoluble drug in the liquisolid formulations, besides choosing a suitable liquid vehicle according to its viscosity and HLB value. Enhanced dissolution rates obtained in the present study in turn indicates increase in oral bioavailability due to increased wetting and surface area available for dissolution. Hence we can conclude that liquisolid tablets of paliperidone was prepared by using Tween 80 (1:1 ratio of drug and Tween 80) and 20 ratio of microcrystalline cellulose and aerosil

200 provide greater release of drug (98.74 % in 60 mins) among all the formulations, and this ratio can be used to enhance the solubility and dissolution rate of poorly water soluble drug pioglitazone hydrochloride. This novel approach to the formulation may be helpful to improve oral bioavailability.

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